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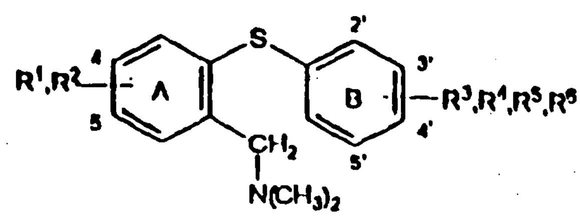
(54) Title: DERIVATES OF N,N-DIMETHYL-2-(ARYLTHIO)BENZYLAMINE, THEIR SALTS, METHODS OF PREPARATION AND THEIR USE IN PHARMACEUTICAL MEDICAMENTS

(57) Abstract



(I)

Derivatives of N,N-dimethyl-2-(arylthio)benzylamine of general formula (I), wherein the substituents R_1 and R_2 in the A ring in the 4 and 5 positions are hydrogen, fluorine, or chlorine atoms, while at least one of them must be a hydrogen atom and further, among the substituents R^3 to R^6 in the B ring two to three are hydrogen atoms, another one is either one fluorine or chlorine atom (only if at least one of the substituents R^1 to R^2 in the A ring is a fluorine or chlorine atom), further, two fluorine or two chlorine atoms, an alkyl with one to three carbon atoms, trifluoromethyl, methylthio, methylsulfinyl, methoxyl or hydroxyl (only if in the B ring there is also a fluorine or chlorine atoms as a substituent), nitro, amino, hydroxymethyl - except the 2 position, carboxyl - except the 3 position, methoxycarbonyl or ethoxycarbonyl group, as well as their salts with pharmacodynamically harmless acids. Methods of preparation of these compounds have been described, as well as some of their pharmacological characteristics and ways of their use in pharmaceutical medicaments based on their ability to selectively influence serotonin transport in the central nervous system.

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Derivatives of N,N-Dimethyl-2-(arylthio)benzylamine, Their Salts, Methods of Preparation and Their Use in Pharmaceutical Medicaments.

Field of Technique

The invention relates to the derivatives of N,N-dimethyl-2-(arylthio)benzylamine and their salts, which selectively inhibit serotonin re-uptake in the brain structures. It is also concerned with the methods of preparation and pharmaceutical medicaments on their basis suitable for treatment of depression and other diseases of the central nervous system, based on serotonin transport defects and serotonin metabolism imbalance in the brain.

Background of the Invention

Besides other compounds, in depression pharmacotherapy tricyclic amines are also used, recently plus some tetracyclic compounds, with a characteristic complex of behavioural features expressed in the term "thymoleptic activity". These compounds, some of which have undesirable cardiotoxic and anticholinergic side effects, are still widely used and are called First-Generation Antidepressants. The progress in biochemical pharmacology, which has led to the knowledge that the influence of antidepressants on the fate of some biogennic amines in brain, noradrenaline in particular, plays its role in the antidepressant effect mechanism, resulted in the synthesis and testing of a large number of monocyclic and bicyclic amines; some of them came to be used in pharmacotherapy of depression and are called Second-Generation Antidepressants.

Since the second half of the 70s, the serotonin transport role in the brain structures in depression ethiology have become understood, and compounds, which besides inhibiting noradrenaline presynaptic re-uptake also substantially inhibit serotonin re-uptake, have been gradually discovered. There has been an effort to find selective inhibitors of serotonin re-uptake with minimum influence on noradrenaline re-uptake. This type of antidepressants is called Third-Generation Antidepressants, and also here a number of monocyclic or bicyclic amines have been found, e.g. citalopram, fluoxetine, paroxetine, fluvoxamine and sertraline (Owen R.T.: Drugs of Today, 28, 439 (1992)), which have been already applied in pharmacotherapy of depression. An accidental discovery of serotonin and noradrenaline re-uptake inhibition (non-selective effect) in case of the plain N,N-dimethyl-2-(phenylthio)benzylamines (Jílek J. et al.: Collect. Czech. Chem. Commun. 54, 1995 (1989)) aroused a bigger interest concerning compounds of this type and manipulation of the structure of the above mentioned basic compound first led to the series of N,N-dimethyl-2-(methoxy- and hydroxyphenylthio)benzylamines, (Jílek J. et. al: Collect. Czech. Chem. Commun. 54, 3294 (1989)), where some compounds clearly suggested selectivity in effect. It was a case of N,N-dimethyl-2-(3-hydroxyphenylthio)benzylamine, in particular, called "moxifetin" (Protiva M.: Drugs of the Future 16, 911 (1991); CS 276004; EP 396,827).

Another selective inhibitor of serotonin re-uptake in the brain structures is N,N-dimethyl-2-(2-hydroxymethyl)phenylthio)benzylamine (VO 93/12080, and particularly N,N-dimethyl-2-(4-(trifluoromethyl)-2-(hydroxymethyl)phenylthio)benzylamine.

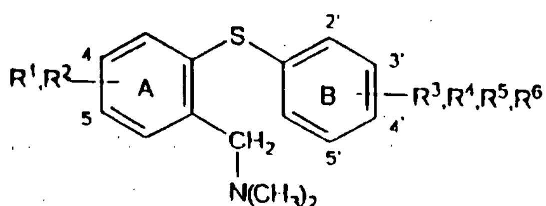
However, even in case of this compound, [^{3}H]serotonin and [^{3}H]noradrenaline re-uptake inhibition in synaptosomal frac-

tions in particular, e.g. of rat cerebral cortex, is not sufficient.

The aim of the invention is to find the modification of the compound on the basis of N,N-dimethyl-2-(phenylthio)benzylamine, which would show higher selectivity and better effects than compounds having been applied up to the present.

Disclosure of the Invention

The grounds of the invention lie in the new derivatives of N,N-dimethyl-2-(arylthio)benzylamine of general formula (I)



(I)

or their salts with inorganic or organic acids which are pharmacodynamically harmless, wherein at least one of the substituents R^1 or R^2 in the A ring in 4 and 5 positions is an hydrogen atom, while the other substituent R^1 or R^2 in the A ring is either a fluorine atom or chlorine atom and wherein two to three among the substituents R^3 to R^6 in the B ring in the 2 to 5 positions are hydrogen atoms, while if the both substituents in the A ring are hydrogen atoms, the substituents in the B ring are either three hydrogen atoms and one substituent formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group, or are two hydrogen atoms, one fluorine or chlorine atom and one substituent formed by an alkyl with one to three carbon

atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino, or methoxy, or hydroxyl group, or are two hydrogen atoms and each of the two remaining substituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group, or are two hydrogen atoms and two fluorine or chlorine atoms; or in case that one substituent in the A ring is either an fluorine atom or chlorine atom, the substituents in the B ring are either two hydrogen atoms and two fluorine or chlorine atoms, or two hydrogen atoms and one fluorine or chlorine atom and one subsituent formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino, or methoxy, or hydroxyl group, or are three hydrogen atoms and one fluorine or chlorine atom, or one of the substituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group.

The anvantageous derivatives of the compound of general formula (I) according to the invention are:

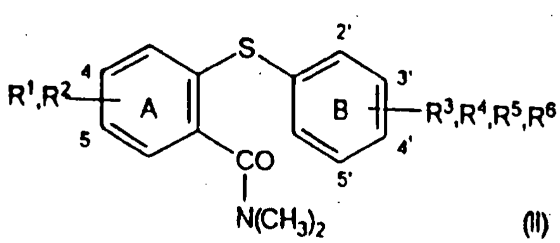
N,N-dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)benzylamine,
N,N-dimethyl-5-chloro-2-(4-(methylthio)phenylthio)benzylamine,
N,N-dimethyl-5-fluoro-2-(4-(methylthio)phenylthio)benzylamine,

N,N-dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzylamine, N,N-dimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzylamine, or N,N-dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzylamine
and their salts with inorganic, or organic acids which are pharmacodynamically harmless.

The structure of the above mentioned compounds suggests that the said specificity of substituents on a diphenylsulfide fragment lies particularly in the presence of a halogen atom in the 5 position of the A ring and in the presence of a 2-amino group or a 4-(methylthio) group in the B ring.

According to the invention, the advantageous compound is N,N-dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)benzylamine, and among its salts particularly oxalate, dihydrochloride and maleate. This compound shows the highest selectivity regarding the comparison of inhibition of serotonin re-uptake and noradrenaline re-uptake in the brain structures, which is apparent from the Table of biological activity (see below).

Derivatives of the compound of general formula (I) can be prepared via various procedures which use the methods of organic synthesis. As for the fundamental procedure, the key intermediate products are N,N-dimethylamides of general formula (II)

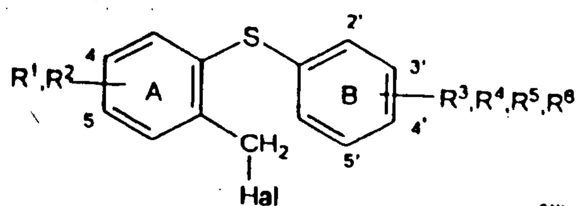


(II)

wherein the substituents R^1 to R^6 are identical to those in formula (I), and besides that, in the B ring can also be

a formyl or dimethylaminocarbonyl group. In the last step of synthesis these amides are reduced by e.g. complex hydrides of the lithium aluminium hydride type, or by diborane, which is advantageously used "in situ", so that in the reaction mixture it is generated by the reaction of sodium borohydride with boron trifluoride etherate. If any of the substituents R^3 to R^6 in the B ring is a formyl, dimethylaminocarbonyl or carboxyl group, according to the invention also such a group is reduced at the same time and provide the derivative of the compound of general formula (I) with a hydroxyl or dimethylaminomethyl group.

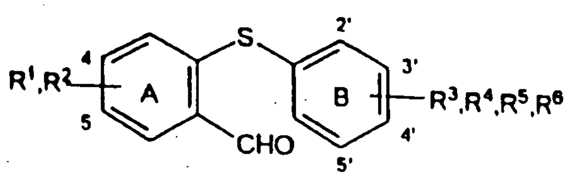
Another method of preparation of the derivatives of the compound (I) according to the invention, uses benzylhalogenides of general formula (III), as an intermediate product in the last step



(III)

wherein Hal is an chlorine or bromine atom and the substituents R^1 to R^6 are identical to the substituents in formula (I). These benzylhalogenides are brought into reaction with dimethylamine in an organic solvent - advantageously in toluene at room temperature.

In yet another advantageous procedure according to the invention, the benzaldehydes of general formula IV



(IV)

wherein the substituents R^1 to R^6 are identical to the substituents in formula (I), in the last step react with dimethylformamide and formic acid at higher temperatures - the advantageous temperature is between 110 and 120^{0}C.

If one of the substituents on the B ring of the compound of general formula (I) according to the invention, shall be methylsulfinyl, the corresponding methylthioderivative is oxidised by hydrogen peroxide in acetic acid at room temperature.

If one of the substituents on the B ring of the compound of general formula (I) according to the invention, shall be esterified carbonyl, i.e. methoxycarbonyl or ethoxycarbonyl, the corresponding carboxyderivative is esterified by methanol or ethanol - advantageously in the presence of hydrogen chloride, or the corresponding trifluoromethylderivative is used, which is hydrolysed with sulfuric acid at 90 to 110^{0}C and then is esterified with the corresponding alcohol.

Finally, if one of the substituents R^3 to R^6 in the B ring of the compound of general formula (I) according to the invention, is hydroxyl, the corresponding methoxyderivative demethylates - anvantageously via heating with hydrobromic acid.

Further, the salts of compounds of general formula (I) according to the invention can anvantageously be prepared via neutralisation of bases with pharmacodynamically harmless inorganic or organic acids.

All derivatives of the compound of general formula (I) according to the invention are of an alkaline nature and their bases are insoluble in water, and mostly are of oily appearance. Neutralisation of all of them with suitable acids

yields their crystalline salts, usually also badly soluble in water; their examples can be hydrochlorides, oxalates or maleates. Providing one substituent on the B ring is carboxyl, the final products are amphoteric, but, however, they also provide the crystalline salts due to the presence of a strong basic amino group.

These salts, or the above mentioned amphoteric "amino acids" are suitable for preparation of oral medical forms, which can be used advantageously in human pharmacotherapy. The affinity of the compounds according to the invention, to serotonergic system conditions the potential use of compounds according to the invention not only in treatment of depression, but also in treatment of migraine, fear or anxiety states, or as anorectics in treatment of obesity.

Examples of the Methods According to the Invention

Some advantageous methods of preparation of the derivatives of compound of general formula (I) according to the invention are demonstrated in the following examples.

Example 1:

N,N-Dimethyl-4-fluoro-2-(3-fluorophenylthio)benzylamine.

a) 8.0 g of 3-fluorothiophenol (Rajšner M. and Protiva M.: Collect. Czech. Chem. Commun. 32, 2021 (1967)) was gradually added to a solution of 9.0 g of potassium hydroxide in 80 ml water and after 10 min of stirring, 1.0 g of powdered copper and 10.6 g of 4-fluoro-2-iodobenzoic acid (Rajšner M. et. al: Collect. Czech. Chem. Commun. 40, 719 (1975)) were added and the mixture was refluxed under stirring for 6 h. After partial cooling, the insoluble fractions were filtered off

by suction and the filtrate was acidified with diluted hydrochloric acid (1:1) under stirring. After 16 h of standing, the product was filtered, washed with water and dried, which yielded 7.5 g of 4-fluoro-2-(3-fluorophenylthio)benzoic acid, which after crystallisation from ethanol melted at 198.5-200^{0}C.

b) 7.6 g of thionylchloride was added under stirring dropwise to a suspension of 7.35 g of 4-fluoro-2-(3-fluorophenylthio)benzoic acid in 60 ml of benzene. After adding two drops of dimethylformamide, the mixture was refluxed for 2 h. The volatile constituents evaporated off *in vacuo*, the residue was added, 2x80 ml of benzene and evaporated *in vacuo*.

Crystallisation of the residue from cyclohexane yielded 7.3 g of 4-fluoro-2-(3-fluorophenylthio)benzoyl chloride with the melting point 91-93^{0}C.

c) A solution of 7.2 g of 4-fluoro-2-(3-fluorophenylthio)-benzoyl chloride in 50 ml of benzene was added dropwise under intensive stirring at 20^{0}C over a period of 5 min to 25 ml of 40% aqueous solution of dimethylamine and the mixture was stirred at room temperature for 3 h. The benzene layer was separated, washed with 2x40 ml of water, dried with potassium carbonate and evaporated *in vacuo*, which yielded 8.2 g of crude oily N,N-dimethyl-4-fluoro-2-(3-fluorophenylthio)benzamide.

d) 2.8 g of sodium borohydride was added to a solution of 8.2 g of crude N,N-dimethyl-4-fluoro-2-(3-fluorophenylthio)-benzamide in 70 ml of tetrahydrofuran and then 10.4 g of boron trifluoride etherate was added dropwise under stirring at room temperature over a period of 15 min. The mixture was stirred at room temperature for 1 h and then was refluxed for 3 h. After cooling, 30 ml of diluted hydrochloric acid (1:1) was added dropwise and the mixture was refluxed for a further 3 h. After cooling, the mixture was alkalised with 20% solution of sodium hydroxide and the product was extrac-

ted with ether. The extract was dried with anhydrous potassium carbonate and was evaporated. The residue (9.2 g) was dissolved in ether and the solution was neutralised with a solution of maleic acid in ether. After 16 h of standing, 6.3 g of N,N-dimethyl-4-fluoro-2-(3-fluorophenylthio)benzylamine hydrogen maleate precipitated. This, after recrystallisation from a mixture of acetone and ether, melted at 159-160^{0}C.

Example 2:

N,N-dimethyl-2-(3,4-difluorophenylthio)benzylamine.

10.0 g (0.068 mol) of 3,4-difluorothiophenol (Červená I.et al.: Collect. Czech. Chem. Commun. 41, 881 (1976)) was gradually added to a solution of 12.65 g of potassium hydroxide in 135 ml of water at 50^{0}C. After 10 min of stirring, 1.0 g of powdered copper and 16.62 g of 2-iodobenzoic acid were added to the mixture. The mixture was refluxed under stirring for 9 h and processed in analogy to example 1/a to obtain 14.20 g (80%) of 2-(3,4-difluorophenylthio)benzoic acid, which after recrystallisation from ethanol melted at 196-198^{0}C.

20.3 g of thionylchloride was added dropwise under stirring to a suspension of 14.0 g of 2-(3,4-difluorophenylthio)-benzoic acid (0.052 mol) in 115 ml of benzene and after adding two drops of dimethylformamide, it was processed in analogy to example 1/b. Crystallisation of the residue (16.7 g) from cyclohexane yielded 13.9 g (93%) of 2-(3,4-difluorophenylthio)benzoyl chloride with the melting point 73-74^{0}C.

A solution of 13.8 g of 2-(3,4-difluorophenylthio)benzoyl-chloride in 96 ml of benzene was added dropwise at temperature not exceeding 8^{0}C and under intensive stirring to 22 ml of 40% aqueous solution of dimethylamine. Then it was pro-

cessed in analogy to example 1/c, which yielded 13.9 g of (98%) crude N,N-dimethyl-2-(3,4-difluorophenylthio)benzamide. 3.4 g of sodium borohydride was added to a solution of 13.8 g of crude N,N-dimethyl-2-(3,4-difluorophenylthio)benzamide (0.047 mol) in 90 ml of tetrahydrofuran and then 13.9 g of boron trifluoride etherate was added dropwise under stirring at 27^{0}C. The mixture was processed in analogy to example 1/d. The residue (15.0 g) of the crude base was dissolved in ether, the solution was filtered and the filtrate was neutralised with a solution of hydrogen chloride in ethanol. 13.3 g of N,N-dimethyl-2-(3,4-difluorophenylthio)-benzylamine hydrochloride was obtained as a result of crystallisation, which after recrystallisation from a mixture of ethanol and ether melted at 153-154^{0}C.

Example 3:

N,N-Dimethyl-4-fluoro-2-(4-fluorophenylthio)benzylamine.

A reaction of 8.6 g of 4-fluoro-2-(4-fluorophenylthio)-benzoic acid (Ger.Offen.2,545,841) in 70 ml of benzene with 12.5 g of thionylchloride and dimethylformamide in analogy to example 1/b, yielded 9.2 g (100%) of 4-fluoro-2-(4-fluorophenylthio)benzoylchloride, which after crystallisation and recrystallisation from a mixture of benzene and petroleum ether melted at 105-106 ^{0}C.

A reaction of 9.0 g of 4-fluoro-2-(4-fluorophenylthio)-benzoyl chloride in 60 ml benzene and 14.5 ml of 40% aqueous solution of dimethylamine, in analogy to example 1/c, yielded 9.26 g (100%) of crude oily N,N-dimethyl-4-fluoro-2-(4-fluorophenylthio)benzamide.

A reaction of crude N,N-dimethyl-4-fluoro-2-(4-fluorophenylthio)benzamide in 60 ml of tetrahydrofuran with 2.3 g of sodium borohydride and 9.3 g of boron trifluoride etherate, in analogy to example 1/d, yielded 8.7 g of oily base, which provided 8.7 g N,N-dimethyl-4-fluoro-2-(4-fluorophenylthio)-

benzylamine hydrogen maleate with the melting point 183-184^{0}C (95% ethanol).

Example 4:

N,N-Dimethyl-5-fluoro-2-(3-fluorophenylthio)benzylamine.

9.0 g of potassium hydroxide in 80 ml of water, 10.6 g of 5-fluoro-2-iodobenzoic acid (Rajšner et. al: Collect. Czech. Chem. Commun. 40, 719 (1975)), 6.3 g 3-fluorothiophenol (Rajšner M. and Protiva M.: Collect. Czech. Chem. Commun. 32, 2021 (1967)) and 1.0 g of copper were refluxed under stirring for 6.5 h and then the mixture was processed in analogy to example 1/a, which after crystallisation from aqueous ethanol yielded 8.9 g of 5-fluoro-2-(3-fluorophenylthio)benzoic acid, melted at 157.5-159^{0}C.

A reaction of 8.75 g of 5-fluoro-2-(3-fluorophenylthio)-benzoic acid with 9.6 g of thionylchloride in 80 ml of benzene, in analogy to example 1/b, yielded 8.2 g of oily 5-fluoro-2-(3-fluorophenylthio)benzoyl chloride.

A solution of 8.0 g of 5-fluoro-2-(3-fluorophenylthio)-benzoyl chloride in 60 ml of benzene and 30 g of 40% aqueous solution of dimethylamine was processed in analogy to example 1/c, which yielded 8.6 g of oily N,N-dimethyl-5-fluoro-2-(3-fluorophenylthio)benzamide.

A reaction of 8.6 g of N,N-dimethyl-5-fluoro-2-(3-fluorophenylthio)benzamide in 70 ml of tetrahydrofuran with 2.8 g of sodium borohydride and 12 g of boron trifluoride etherate and then through neutralisation with a solution of maleic acid in ether, in analogy to example 1/d, yielded 5.3 g of N,N-dimethyl-5-fluoro-2-(3-fluorophenylthio)benzylamine hydrogen maleate, which after crystallisation from a mixture of acetone and ether melted at 117.5-118.5^{0}C.

Example 5

N,N-Dimethyl-5-fluoro-2-(4-fluorophenylthio)benzylamine.

9.0 g of potassium hydroxide in 80 ml of water, 10.6 g of 5-fluoro-2-iodobenzoic acid, 5.5 g of 4-fluorothiophenol (Rajšner et. al: Česk. Farm. 11, 451 (1962)), and 1.0 g of copper were refluxed for 7 h and proccesed in analogy to example 1/a. After crystallisation from ethanol, 9.3 g of 5-fluoro-2-(4-fluorophenylthio)benzoic acid was obtained, which melted at 206-207.5^{0}C.

A reaction of 9.15 g of 5-fluoro-2-(4-fluorophenylthio)-benzoic acid with 11.7 g of thionylchloride in 100 ml of benzene and dimethylformamide, in analogy to example 1/b and crystallisation from cyclohexane yielded 9.85 g of 5-fluoro-2-(4-fluorophenylthio)benzoyl chloride, m.p. 90-91.5^{0}C.

A reaction of 9.7 g of 5-fluoro-2-(4-fluorophenylthio)-benzoyl chloride in 50 ml of benzene with 31 g of 40% aqueous dimethylamine, in analogy to example 1/c, yielded 10.1 g of oily N,N-dimethyl-5-fluoro-2-(4-fluorophenylthio)-benzamide.

A reaction of 10.1 g of oily N,N-dimethyl-5-fluoro-2-(4-fluorophenylthio)benzamide in 70 ml of tetrahydrofuran with 2.8 g of sodium borohydride and 10.0 g of boron trifluoride etherate, in analogy to example 1/d, yielded 6.6 g of crystalline N,N-dimethyl-5-fluoro-2-(4-fluorophenylthio)benzyl-amine hydrogen maleate, which after recrystallisation from a mixture of acetone and ether melted at 135.5-136.5^{0}C.

Example 6:

N,N-Dimethyl-5-fluoro-2-(3,4-difluorophenylthio)benzylamine.

a) A reaction of 5.7 g of potassium hydroxide in 62 ml of water with 4.50 g of 3.4-difluorothiophenol, 7.98 g of

5-fluoro-2-iodobenzoic acid, 0.45 g of copper, in analogy to example 1/a, yielded 7.22 g of 5-fluoro-2-(3,4-difluorophenylthio)benzoic acid with melting point 181-182^{0}C.

b) A reaction of 7.0 g of 5-fluoro-2-(3,4-difluorophenylthio)benzoic acid with 7.4 g of thionylchloride in 60 ml of benzene, in analogy to the example 1/b, yielded 7.2 g (97%) of crystalline 5-fluoro-2-(3,4-difluorophenylthio)benzoyl chloride, melting at 77-78^{0}C.

c) A reaction of 7.0 g of 5-fluoro-2-(3,4-difluorophenylthio)benzoyl chloride in 50 ml of benzene with 12 ml of 40% aqueous dimethylamine, in analogy to example 1/c, yielded 6.9 g (96%) of oily N,N-dimethyl-5-fluoro-2-(3,4-difluorophenylthio)benzamide.

d) 6.8 g of oily N,N-dimethyl-5-fluoro-2-(3,4-difluorophenylthio)benzamide in 42 ml of tetrahydrofuran with 1.56 g of sodium borohydride and 6.45 g of boron trifluoride etherate were brought into reaction in analogy to example 1/d. The obtained crude base was extracted from an aqueous solution of 3x25 ml of benzene. Neutralisation with a solution of hydrogen chloride in ethanol yielded 6.4 g of crystalline N,N-dimethyl-5-fluoro-2-(3,4-difluorophenylthio)-benzylamine hydrochloride, which after crystallisation from ethanol melted at 148-150^{0}C.

Example 7:

N,N-Dimethyl-2-(2,4-dichlorophenylthio)benzylamine.

a) 20 ml of thionylchloride was added to a solution of 13.6 g of 2-(2,4-dichlorophenylthio)benzoic acid (Šindelář K. et al.: Collect. Czech. Chem. Commun. 38, 3321 (1973)) in 100 ml of toluene and the mixture was refluxed for 3 h. The volatile constituents evaporated off *in vacuo*, which yielded 14.3 g of crystalline crude 2-(2,4-dichlorophenylthio)-benzoyl chloride, which after crystallisation from petroleum ether melted at 91-93^{0}C.

b) A solution of 14.3 g of 2-(2,4-dichlorophenylthio)-benzoyl chloride in 200 ml of dioxane was saturated with gaseous dimethylamine over a period of 2 h under occasional external cooling with icy water. After 16 h of standing, the volatile constituents evaporated off *in vacuo* and the residue was extracted between water and benzene. The benzene phase was dried with magnesium sulfate and evaporated *in vacuo*, to obtain 13.7 g of N,N-dimethyl-2-(2,4-dichlorophenylthio)benzamide, which after crystallisation from a mixture of benzene and petroleum ether melted at 120-122^{0}C.

c) 3.0 g of sodium borohydride was added to a solution of 11.83 g of N,N-dimethyl-2-(2,4-dichlorophenylthio)benzamide in 60 ml of tetrahydrofuran and then 10 ml of boron trifluoride etherate was added dropwise over a period of 40 min. The reaction mixture was processed in analogy to example ple 1/d. The crude base was dissolved in chloroform and purified by filtration on a 150 g silica gel column. After evaporating the chloroform, the obtained crude base was neutralised using 5.0 g of oxalic acid dihydrate in 50 ml of ethanol, which yielded 10.6 g of crystalline N,N-dimethyl-2-(2,4-dichlorophenylthio)benzylamine hydrogen oxalate, melting at 208-211^{0}C.

Example 8:

N,N-Dimethyl-2-(2,5-dichlorophenylthio)benzylamine.

A reaction of 11.0 g of 2-(2,5-dichlorophenylthio)benzoic acid (Šindelář K. et. al: Collect. Czech. Chem. Commun. 38, 3321 (1973)) in a mixture of 100 ml of toluene and 20 ml of thionylchloride was carried out in analogy to example 1/b, which yielded 12.0 g of 2-(2,5-dichlorophenylthio)benzoyl chloride, which after crystallisation from cyclohexane melted at 104-105.5^{0}C.

A reaction of 12.0 g of 2-(2,5-dichlorophenylthio)benzoyl

chloride in 200 ml of dioxane with gaseous dimethylamine carried out in analogy to example 7/b, yielded 11.2 g (93%) of crystalline N,N-dimethyl-2-(2,5-dichlorophenylthio)benzamide, which after crystallisation from a mixture of benzene and petroleum ether melted at 124-126^{0}C.

2.6 g of sodium borohydride was added to a solution of 10.2 g of N,N-dimethyl-2-(2,5-dichlorophenylthio)benzamide in 60 ml of tetrahydrofuran and then 8.6 ml of boron trifluoride etherate was added dropwise at room temperature under nitrogen over a period of 30 min. The reaction mixture was processed in analogical procedure to example 1/d to obtain the crude oily base (9.7 g). The base was neutralised using 4.7 g of oxalic acid dihydrate in ethanol. The subsequent crystallisation yielded 9.0 g (73 %) N,N-dimethyl-2-(2,5-dichlorophenylthio)benzylamine hydrogen oxalate which melted at 180-182.5^{0}C.

Example 9:

N,N-Dimethyl-2-(3,4-dichlorophenylthio)benzylamine.

A reaction of 14.2 g of 2-(3,4-dichlorophenylthio)benzoic acid (Červená I. and others: Collect. Czech. Chem. Commun. 41, 881 (1976)) in 180 ml of benzene with 15.2 g of thionylchloride, carried out in analogy to example 1/b, yielded 15.5 g of crude crystalline 2-(3,4-dichlorophenylthio)benzoyl chloride, which after crystallisation from cyclohexane melted at 104.5-105.5^{0}C.

15.3 g of 2-(3,4-dichlorophenylthio)benzoyl chloride in 100 ml of benzene was mixed with 32 g of 40% aqueous solution of dimethylamine under mild cooling over a period of 10 min. The mixture was stirred for 4 h at room temperature and evaporated *in vacuo*. The residue contained 15.3 g of oily N,N-dimethyl-2-(3,4-dichlorophenylthio)benzamide.

A reaction of 15.3 g of oily N,N-dimethyl-2-(3,4-dichloro-

phenylthio)benzamide in 100 ml of tetrahydrofuran with 4.5 g of sodium borohydride and 15.0 g of boron trifluoride etherate under nitrogen and the procedure carried out in analogy to example 1/d yielded crystalline N,N-dimethyl-2-(3,4-dichlorophenylthio)benzylamine hydrogen maleate, which after crystallisation from a mixture of acetone and ether melted at 127.5-128.5 ^{0}C.

Example 10:

N,N-Dimethyl-2-(3,5-dichlorophenylthio)benzylamine.

A suspension of 3,5-dichloroaniline hydrochloride obtained from 29.0 g of 3,5-dichloroaniline and 75 ml of diluted hydrochloric acid (1:1) was diazotized under stirring at 0-5 ^{0}C with a solution of 13.7 g of sodium nitrite in 30 ml of water. 0.2 g of nickel sulfate was added to a solution of the diazonium salt and the cooled mixture was added in small amounts to a solution of 35 g of potassium xanthate in 45 ml of water kept between 40-45 ^{0}C. After having added everything, this temperature was kept for a further 1 h. After cooling, the mixture was extracted with ether, the ethereal extract was washed with 50 ml of 10% solution of sodium hydroxide, dried with calcium chloride and ether evaporated off. The residue was dissolved in 115 ml of ethanol and 45 g of potassium hydroxide was slowly added to the boiling solution. The mixture was refluxed for 8 h, the ethanol was distilled off and 160 ml of 3M sulfuric acid was added to the residue at a temperature of 25 ^{0}C maximum. The oily product was extracted with the ether and the extract was evaporated, which yielded 16.1 g of semicrystalline crude 3,5-dichlorothiophenol.

A reaction of 16.1 g of crude 3,5-dichlorothiophenol, 24 g of 2-iodobenzoic acid and 1.65 g of copper with 20.8 g of potassium hydroxide in 225 ml of water at 50-60 ^{0}C, refluxing

under stirring for 9 h and then processing in analogy to example 1/a, yielded 24 g (90%) of 2-(3,5-dichlorophenylthio)benzoic acid, which after crystallisation from ethanol melted at 198-200^{0}C.

22 ml of thionylchloride was added under stirring over a period of 1.5 h to a suspension of 24.0 g of 2-(3,5-dichlorophenylthio)benzoic acid in 220 ml of benzene heated up to 70^{0}C. The mixture was then processed in analogy to example 1/b. Crystallisation from cyclohexane yielded 23.2 g of 2-(3,5-dichlorophenylthio)benzoyl chloride with melting point 104-107^{0}C.

A solution of 23.2 g of 2-(3,5-dichlorophenylthio)benzoyl chloride in 160 ml of toluene was added under intensive stirring at 4-6^{0}C over a period of 1 h to 80 ml of 40% aqueous solution of dimethylamine. The filtrate was stirred a further 2 h at room temperature. The toluene phase was separated, washed with water and dried with potassium carbonate which was filtered off. The mixture was evaporated *in vacuo*, which yielded 17.5 g of oily N,N-dimethyl-2-(3,5-dichlorophenylthio)benzamide, which crystallised on standing and after recrystallisation from a mixture of benzene and petroleum ether melted at 120-122^{0}C.

3.6 g of sodium borohydride was added to a solution of 18.0 g N,N-dimethyl-2-(3,5-dichlorophenylthio)benzamide in 125 ml of tetrahydrofuran and then 18.3 g of boron trifluoride etherate was added dropwise under nitrogen at 20-27^{0}C over a period of 1 h. The mixture was then processed in analogy to example 1/d. The residue of the crude base was dissolved in ether, the solution was filtered and the filtrate was neutralised with a solution of hydrogen chloride in ether. The precipitated crystalline N,N-dimethyl-2-(3,5-dichlorophenylthio)benzylamine hydrochloride after recrystallisation from a mixture of ethanol and ether melted at 185-189^{0}C.

Example 11:

N,N-Dimethyl-5-chloro-2-(2,4-dichlorophenylthio)benzylamine.

8.95 g of 2,4-dichlorothiophenol (Sparke M.B. et. al: J. Am. Chem. Soc. 75, 4907 (1953)), 14.1 g of 5-chloro-2-iodobenzoic acid (Pelz K. et. al: Collect. Czech. Chem. Commun. 33, 1852 (1968)) and 2.5 g of copper were step by step added to a solution of 9.1 g of potassium hydroxide in 100 ml of water and the mixture was refluxed under stirring for 7.5 h. Then the mixture was diluted with 150 ml of hot water, filtered and further processed in analogy to example 1/a. Crystallisation from ethanol yielded 14.9 g (89%) of 5-chloro-2-(2,4-dichlorophenylthio)benzoic acid, m.p. 188-191^{0}C.

A mixture of 14.8 g of 5-chloro-2-(2,4-dichlorophenylthio)-benzoic acid in 100 ml of toluene and 20 ml of thionylchloride was heated up to 80^{0}C under stirring under reflux condenser and then was processed in analogy to example 1/b, which yielded 12.4 g (80%) of crude crystalline 5-chloro-2-(2,4-dichlorophenylthio)benzoylchloride, which after crystallisation from cyclohexane melted at 129-132^{0}C.

A reaction of 12.0 g of crude 5-chloro-2-(2,4-dichlorophenylthio)benzoyl chloride in 200 ml of dioxane with gaseous dimethylamine in analogy to example 7/b yielded the crude amide, which was dissolved in 60 ml of chloroform and filtered on a 130 g silica gel column. The column was eluted with chloroform, the solvent evaporated off to obtain 10.3 g (84%) of crystalline N,N-dimethyl-5-chloro-2-(2,4-dichlorophenylthio)benzamide, which after crystallisation from a mixture of benzene and petroleum ether melted at 96-97^{0}C.

8.6 g of N,N-dimethyl-5-chloro-2-(2,4-dichlorophenylthio)-benzamide in 50 ml of tetrahydrofuran, 2.0 g of sodium borohydride and 6.6 ml of boron trifluoride etherate was processed in analogy to example 1/d, which yielded 7.4 g of oily N,N-dimethyl-5-chloro-2-(2,4-dichlorophenylthio)benzylamine.

This was dissolved in ethanol and neutralised with a solution of hydrogen chloride in ether, which yielded 6.86 g of the crystalline hydrochloride. This, after crystallisation from a mixture of methanol and ethanol, melted at 258-261^{0}C.

Example 12:

N,N-Dimethyl-5-chloro-2-(2,5-dichlorophenylthio)benzylamine.

a) 2.95 g of 2,5-dichlorothiophenol (Šindelář K. et al.: Collect. Czech. Chem. Commun. 38, 3321 (1973)), 14.12 g of 5-chloro-2-iodobenzoic acid and 2.5 g of copper were step by step added to a solution of 9.1 g of potassium hydroxide in 100 ml of water and the mixture was refluxed for 9 h. Vhile still hot, it was diluted with 50 ml of hot water and filtered. After cooling, the filtrate was acidified with 18 ml of diluted hydrochloric acid (1:1) and left standing for 16 h at 0^{0}C. The precipitated crude 5-chloro-2-(2,5-dichlorophenylthio)benzoic acid was filtered by suction and dissolved in 100 ml of dimethylformamide at 80^{0}C. The solution was filtered, and the pure acid precipitated by diluting of the cold filtrate with 500 ml of water. This was filtered by suction and its recrystallisation from ethanol yielded 10.90 g (65%) of 5-chloro-2-(2,5-dichlorophenylthio)benzoic acid, m.p. 216-218^{0}C.

b) A reaction of 10.9 g of 5-chloro-2-(2,5-dichlorophenylthio)benzoic acid in 100 ml of toluene with 20 ml of thionylchloride carried out in analogy to example 1/b and after crystallisation yielded 11.0 g of 5-chloro-2-(2,5-dichlorophenylthio)benzoyl chloride, which melted at 105-106^{0}C.

c) A reaction of 11.0 g of 5-chloro-2-(2,5-dichlorophenylthio)benzoyl chloride in 200 ml of dioxane with gaseous dimethylamine, carried out in analogy to example 7/b, yielded 10.7 g (90%) of crystalline N,N-dimethyl-5-chloro-2-(2,5-dichlorophenylthio)benzamide, which after crystallisation from

a mixture of cyclohexane and petroleum ether melted at 92-93^{0}C.

d) A reaction of 10.2 g of N,N-dimethyl-5-chloro-2-(2,5-dichlorophenylthio)benzamide in 60 ml of tetrahydrofuran with 2.58 g of sodium borohydride and 8.6 ml of boron trifluoride etherate, carried out in analogy to example 1/d, yielded the oily base, which was dissolved in 12 ml of ethanol and neutralised by the addition of 10 ml of hydrogen chloride in ether. Crystallisation from ethanol yielded 8.1 g (75%) of N,N-dimethyl-5-chloro-2-(2,5-dichlorophenylthio)benzylamine hydrochloride, m.p. 252-255^{0}C (in sealed capillary).

Example 13:

N,N-Dimethyl-5-chloro-2-(3,4-dichlorophenylthio)benzylamine.

A reaction of 5.6 g of potassium hydroxide in 100 ml of water with 5.37 g of 3,4-dichlorothiophenol (Červená I. et al.: Collect. Czech. Chem. Commun. 41, 881 (1976)), 8.48 g of 5-chloro-2-iodobenzoic acid and 2.5 g of copper, carried out in analogy to example 1/a, yielded 9.1 g (91%) of 5-chloro-2-(3,4-dichlorophenylthio)benzoic acid (m.p. 223-227^{0}C), which after crystallisation from ethanol melted at 225-227^0 C.

A reaction of 8.6 g of 5-chloro-2-(3,4-dichlorophenylthio)-benzoic acid with 20 ml of thionylchloride, carried out in analogy to example 1/b, yielded crystalline 5-chloro-2-(3,4-dichlorophenylthio)benzoyl chloride (100% yield), which after crystallisation from cyclohexane melted at 98-101^0.

A solution of 9.0 g of 5-chloro-2-(3,4-dichlorophenylthio)-benzoyl chloride in 150 ml of dioxane was saturated with gaseous dimethylamine over a period 1.5 h and processed in analogy to example 7/b. The benzene phase was washed with diluted solution of sodium carbonate and with water, dried

with magnesium sulfate, then filtered and evaporated *in vacuo*. The residue was dissolved in chloroform and the solution was filtered on a 75 g silica gel column. Evaporating of the filtrate yielded 7.43 g (80%) of oily N,N-dimethyl-5-chloro-2-(3,4-dichlorophenylthio)benzamide.

1.6 g of sodium borohydride was added to a solution of 6.8 g of oily N,N-dimethyl-5-chloro-2-(3,4-dichlorophenylthio)benzamide in 60 ml of tetrahydrofuran and then 8 ml of boron trifluoride etherate was added dropwise under nitrogen and under stirring over a period of 1 h. The mixture was processed in analogy to example 1/d. Neutralisation with a solution of hydrogen chloride in ether yielded 5.25 g (74%) of crystalline N,N-dimethyl-5-chloro-2-(3,4-dichlorophenylthio)benzylamine hydrochloride, which after recrystallisation from a mixture of ethanol and ether melted at 203-207^{0}C.

Example 14:

N,N-Dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzylamine.

a) A reaction of 5.7 g of potassium hydroxide in 65 ml of water with 5.52 g of 2,4-dichlorothiophenol, 7.98 g of 5-fluoro-2-iodobenzoic acid and 0.45 g of copper, carried out in analogy to example 1/a, yielded2-(2,4-dichlorophenylthio)-5-fluorobenzoic acid, which was filtered by suction and recrystallised from ethanol, which yielded 8.32 g of the acid, m.p. 198.5-199.5^{0}C.

b) 9.92 g of thionylchloride was added dropwise under stirring at 60^{0}C to a suspension of 8.15 g of 2-(2,4-dichlorophenylthio)-5-fluorobenzoic acid in 55 ml of benzene, and the resulting solution was processed in analogy to example 1/b. Crystallisation from cyclohexane yielded 8.3 g of 2-(2,4-dichlorophenylthio)-5-fluorobenzoyl chloride, m.p. 85-86^{0}C.

c) A solution of 8.1 g of 2-(2,4-dichlorophenylthio)-5-

fluorobenzoyl chloride in 50 ml of benzene was added dropwise under intensive stirring at 8^0C to 11 ml of 40% aqueous solution of dimethylamine. The mixture was stirred for a further 2 h at 15^0C and then was processed in analogy to example 1/c, which yielded 8.3 g (100%) of oily N,N-dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzamide.

d) 7.6 g of oily N,N-dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzamide in 45 ml of tetrahydrofuran, 1.6 g of sodium borohydride and 6.51 g of boron trifluoride etherate reacted in analogy to example 1/d, the gained residue of the crude base was dissolved in ether, the solution was filtered and the filtrate neutralised with a solution of hydrogen chloride in ether. Crystallisation from ethanol yielded 7.05 g of N,N-dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzamine hydrochloride, which after crystallisation from ethanol melted at 209-212^0C.

Example 15:

N,N-Dimethyl-2-(2,5-dichlorophenylthio)-5-fluorobenzamine.

A reaction of 5.7 g of potassium hydroxide in 65 ml of water with 5.52 g of 2,5-dichlorothiophenol, 7.98 g of 5-fluoro-2-iodobenzoic acid and 0.45 g of copper, carried out in analogy to example 1a, yielded 9.05 g (95%) of 2-(2,5-dichlorophenylthio)-5-fluorobenzoic acid, m. p. 224-227^0C.

In analogy to example 1/b, a reaction of 8.9 g of 2-(2,5-dichlorophenylthio)-5-fluorobenzoic acid with 10.8 g of thionylchloride in 60 ml of benzene and dimethylformamide provided 8.45 g (90%) of crystalline 2-(2,5-dichlorophenylthio)-5-fluorobenzoyl chloride, which after recrystallisation from cyclohexane melted at 110-111^0C.

In analogy to example 1/c, a reaction of a solution of 8.2 g of 2-(2,5-dichlorophenylthio)-5-fluorobenzoyl chloride with 11 ml of 40% aqueous dimethylamine and crystallisation

from methanol yielded 7.87 g (94%) of crystalline N,N-dimethyl-2-(2,5-dichlorophenylthio)-5-fluorobenzamide, m. p. 98-99^{0}C.

A reaction of 7.6 g of N,N-dimethyl-2-(2,5-dichlorophenylthio)-5-fluorobenzamide in 45 ml of tetrahydrofuran with 1,6 g of sodium borohydride and 6.51 g of boron trifluoride etherate, carried out in analogy to example 14/d, yielded 7.05 g of N,N-dimethyl-2-(2,5-dichlorophenylthio)-5-fluorobenzylamine hydrochloride, which after crystallisation from ethanol melted at 198-201 ^{0}C.

Example 16:

N,N-Ddimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzylamine.

In analogy to example 1a, a reaction of 5.7 g of potassium hydroxide in 70 ml of water with 5.52 g of 3,4-trichlorothiophenol, 7.98 g of 5-fluoro-2-iodobenzoic acid and 0.45 g of copper yielded 8.2 g (86%) of crystalline 2-(3,4-dichlorophenylthio)-5-fluorobenzoic acid, which after crystallisation from ethanol melted at 196-197^{0}C.

In analogy to example 1/b, a reaction of a suspension of 8.0 g of 2-(3,4-dichlorophenylthio)-5-fluorobenzoic acid in 60 ml of benzene with 9.7 g of thionylchloride and dimethylformamide yielded 8.3 g (98%) of crystalline 2-(3,4-dichlorophenylthio)-5-fluorobenzoyl chloride, which after crystallisation from cyclohexane melted at 72-73^{0}C.

A reaction of 8.1 g of 2-(3,4-dichlorophenylthio)-5-fluorobenzoyl chloride in 50 ml of benzene with 13 ml of 40% aqueous dimethylamine, carried out in analogy to example 1/c, yielded 7.6 g (92%) of oily N,N-dimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzamide.

A reaction of 7.6 g of oily N,N-dimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzamide in 50 ml of tetrahydrogenfuran, 1.57 g of sodium borohydride and 6.5 g of boron tri-

fluoride etherate was carried out in analogy to example 14/d and after 16 h of standing, the precipitated crude hydrochloride was filtered by suction and crystallised from ethanol, which yielded 5.5 g of N,N-dimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzylamine, m.p. 178-180^{0}C.

Example 17:

N,N-Dimethyl-2-(3-methylphenylthio)-5-fluorobenzylamine.

60 g of thionylchloride was added dropwise under stirring over a period of 20 min to a solution of 42.6 g of 2-(3-methylphenylthio)benzoic acid (Protiva M. et. al: Collect. Czech. Chem. Commun. 47, 3134 (1982)) in 300 ml of benzene and was processed in analogy to example 1/b. Crystallisation from cyclohexane yielded 45.9 g of 2-(3-methylphenylthio)-benzoyl chloride, m.p. 78-79^{0}C.

A solution of 13.5 g of 2-(3-methylphenylthio)benzoyl chloride was mixed with 50 ml of 40% aqueous dimethylamine under intensive stirring at 10^{0}C over a period of 20 min. The solution was stirred for 3 h at room temperature and was processed in analogy to example 1/c, which yielded 13.9 g of crude N,N-dimethyl-2-(3-methylphenylthio)benzamide.

4.3 g of 90% sodium borohydride was added to a solution of 13.90 g of crude N,N-dimethyl-2-(3-methylphenylthio)benzamide in 90 ml of tetrahydrofuran, then 15 g of boron trifluoride etherate was added dropwise at room temperature over a period 20 min and the mixture was processed in analogy to example 1/d. The crude base was dissolved in ether and neutralised with a solution of maleic acid in acetone. On standing there crystallised 9.83 g of N,N-dimethyl-2-(3-methylphenylthio)benzylamine hydrogen maleate, m.p. 109-111^{0}C.

Example 18:

N,N-Dimethyl-4-fluoro-2-(4-isopropylphenylthio)benzylamine.

One drop of dimethylformamide was added to a suspension of 22.0 g of 4-fluoro-2-(4-isopropylphenylthio)benzoic acid (Protiva M. et al.: Collect. Czech. Chem. Commun. 51, 698 (1986)) in 200 ml of benzene, then 30 g of thionylchloride was added dropwise under stirring over a period of 5 min and the mixture was processed in analogy to example 1b, which yielded 21.4 g (91%) of crude oily 4-fluoro-2-(4-isopropylphenylthio)benzoyl chloride.

A solution of 20.0 g of crude 4-fluoro-2-(4-isopropylphenylthio)benzoyl chloride in 160 ml of benzene was saturated with gaseous dimethylamine at 12-16^{0}C until its weight addition was 22.5 g (1h). The mixture was stirred for a further 1 h at 12-16^{0}C and then washed with water, dried with calcium chloride and filtered. The filtrate was evaporated *in vacuo*. The oily residue was left standing to crystallise (14 days). After addition of petroleum ether it was filtered by suction, which yielded 13.2 g (64%) of N,N-dimethyl-4-fluoro-2-(4-isopropylphenylthio)benzamide, which after recrystallisation from n-hexane melted at 54-55^{0}C.

2.25 g of sodium borohydride was added to a solution of 12.2 g of N,N-dimethyl-4-fluoro-2-(4-isopropylphenylthio)-benzamide, then 11.2 g of boron trifluoride etherate was added dropwise under nitrogen at 20-25^{0}C over a period of 30 min and the mixture was processed in analogy to example 1/d, which yielded 12.0 g (100%) of oily base. This was dissolved in 20 ml of ether and the solution was mixed with a solution of 4.5 g of maleic acid in 10 ml of ethanol. By cooling 13.8 g of N,N-dimethyl-4-fluoro-2-(4-isopropylphenylthio)benzylamine hydrogen maleate crystallised, which after recrystallisation from a mixture of ethanol and ether melted at 117-118^{0}C.

Example 19:

N,N-Dimethyl-2-(2-(trifluoromethyl)phenylthio)benzylamine.

7.0 g of 2-(trifluoromethyl)thiophenol (Sharghi N. and Lalezari I.: J. Chem. Eng. Data 11, 612 (1966), Chem. Abstr. 66, 10690 (1967)), 9.75 g of 2-iodobenzoic acid and 2.2 g of copper were step by step added to a solution of 7.3 g of potassium hydroxide in 80 ml of water, the mixture was refluxed under stirring for 10 h and then was processed in analogy to example 12/a. 11.4 g of 2-(2-(trifluoromethyl)phenylthio)benzoic acid was obtained, which after recrystallisation from benzene melted at 170-174^{0}C.

A reaction of 10.5 g of 2-(2-(trifluoromethyl)phenylthio)-benzoic acid in 100 ml of benzene with 10 ml of thionylchloride, carried out in analogy to example 1/b, yielded 10.0 g crude 2-(2-(trifluoromethyl)phenylthio)benzyol chloride, which after crystallisation from cyclohexane melted at 70-73^{0}C.

A solution of 10.0 g of 2-(2-(trifluoromethyl)phenylthio)-benzoyl chloride in 100 ml of dioxane was saturated with gaseous dimethylamine under external cooling over a period of 1 h. After 16 h of standing, the solvent evaporated *in vacuo* and the oily residue was crude N,N-dimethyl-2-(2-(trifluoromethyl)phenylthio)benzamide.

A reaction of 9.5 g of oily N,N-dimethyl-2-(2-(trifluoromethyl)phenylthio)benzamide in 50 ml of tetrahydrofuran with 2.42 g of sodium borohydride and 9.0 g of boron trifluoride etherate, carried out in analogy to example 1/d, yielded the crude base, which was purified by filtration on a 200 g silica gel column - for eluting a mixture of toluene, chloroform and chloroform saturated with ammonia was used. Evaporating the filtrate yielded 8.7 g (96%) of the chromatographically homogeneous base. Its neutralisation with oxalic acid dihydrate in ethanol yielded 8.5 g of crystalline N,N-dimethyl-2-(2-(trifluoromethyl)phenylthio)benzylamine, which after crystallisation from ethanol melted at 145-147^{0}C.

Example 20:

N,N-Dimethyl-2-(3-(trifluoromethyl)phenylthio)benzylamine.

82.4 g of thionylchloride was added at 60°C to a suspension of 63.4 g of 2-(3-(trifluoromethyl)phenylthio)benzoic acid (Peltz K. et al.: Collect. Czech. Chem. Commun. 34, 3936 (1969)) in 470 ml of benzene. The mixture was refluxed for 2 h and processed in analogy to example 1/b. The product was crystallised from cyclohexane, which yielded 63.2 g (94%) of crystalline 2-(3-(trifluoromethyl)phenylthio)benzoyl chloride, m. p. 85-86°C.

A solution of 63.2 g of 2-(3-(trifluoromethyl)phenylthio)-benzoyl chloride in 400 ml of benzene was mixed together with 90 g of 40% aqueous dimethylamine under intensive stirring at 5°C. The mixture was stirred for 1 h and after standing for 1 h at room temperature, it was processed in analogy to example 1/c, which yielded 64.6 g (100%) of oily N,N-dimethyl-2-(3-(trifluoromethyl)phenylthio)benzamide.

A reaction of 64.6 g of oily N,N-dimethyl-2-(3-(trifluoromethyl)phenylthio)benzamide in 400 ml of tetrahydrofuran with 11.2 g of sodium borohydride and 58.6 g of boron trifluoride etherate, carried out in analogy to example 1/d, yielded the crude base, which was dissolved in ether, filtered and neutralised with a solution of hydrogen chloride in ether. 62.6 g (90%) of N,N-dimethyl-2-(3-(trifluoromethyl)-phenylthio)benzylamine hydrochloride precipitated, which after crystallisation from a mixture of ethanol and ether melted at 165-167°C.

Example 21:

N,N-Dimethyl-2-(4-(trifluoromethyl)phenylthio)benzylamine.

A reaction of 7.6 g of crude 2-(4-(trifluoromethyl)phenyl-

thio)benzoic acid (GB 925,539) in 50 ml of toluene with 20 ml of thionylchloride, carried out in analogy to example 7/a, yielded 8.1 g of crude 2-(4-(trifluoromethyl)phenylthio)-benzoyl chloride, which after crystallisation from cyclohexane melted at 66-68^{0}C.

A reaction of 8.1 g of crude 2-(4-(trifluoromethyl)phenylthio)benzoyl chloride in 75 ml of dioxane with gaseous dimethylamine, carried out in analogy to example 7/b, yielded 7.52 g of oily N,N-dimethyl-2-(4-(trifluoromethyl)phenylthio)benzamide.

A solution of 7.5 g of N,N-dimethyl-2-(4-(trifluoromethyl)-phenylthio)benzamide in 45 ml of tetrahydrofuran was reduced by 1.3 g of sodium borohydride and 6.8 ml of boron trifluoride etherate. The reaction mixture was processed in analogy to example 1/d to obtain the oily base. The base was neutralised with a solution of 4.1 g of oxalic acid dihydrate in 30 ml of ethanol. By addition of 50 ml of ether, crystalline N,N-dimethyl-2-(4-(trifluoromethyl)phenylthio)benzylamine hydrogenoxalate was obtained, which crystallised in two crystalline modifications: the lower melting one - m.p. 166-170^{0}C, and the higher melting one - m.p. 178-182^{0}C.

Example 22:

N,N-Dimethyl-5-fluoro-2-(4-(trifluoromethyl)phenylthio)-benzylamine.

A reaction of 11.2 g of potassium hydroxide in 120 g of water with 14.4 g of crude 4-(trifluoromethyl)-2-nitrothiophenol [obtained by reduction of bis(4-(trifluoromethyl)-2-nitrophenyl)disulfide (Šindelář K. et. al: Collect. Czech. Chem. Commun. 46, 118 (1981)) by glucose when using described procedure (DRP 204,450)], 17.1 g of 5-fluoro-2-iodobenzoic acid and 1.5 g cooper, carried out in analogy to example 1/a, and crystallisation from a mixture of benzene

and cyclohexane yielded 10.5 g (45%) of 5-fluoro-2-(4-(trifluoromethyl)-2-nitrophenylthio)benzoic acid with melting point 156-159 ^{0}C.

A mixture of 10.1 g of 5-fluoro-2-(4-(trifluoromethyl)-2-nitrophenylthio)benzoic acid, 60 ml of ethanol, 5.1 g of hydrazine hydrate, 0.6 g of filtration charcoal and 0.2 g of ferric chloride hexahydrate was refluxed for 11 h and filtered. Ethanol contained in the filtrate evaporated off *in vacuo*. The residue was dissolved in a diluted solution of sodium hydroxide and acidified with acetic acid to obtain 8.4 g of 2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzoic acid, which after crystallisation from a mixture of benzene, ethanol and petroleum ether melted at 191-193 ^{0}C.

A solution of 2.2 g of sodium nitrite in 5 ml of water was slowly added dropwise under stirring at 0 ^{0}C to a solution of 8.0 g of 2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzoic acid and 4.2 ml of sulfuric acid in 70 ml of ethanol. The mixture was stirred at the given temperature for a further 15 min, then 4.5 g of sodium hypophosphite monohydrate in 5 ml of water, 0.2 g of copper and 30 ml of ethanol were added and the mixture was refluxed for 1.5 h. After filtration, the filtrate was evaporated *in vacuo*, the residue was combined with water and filtered by suction. The solid phase was extracted with boiling ethanol, the insoluble fraction was filtered off and the filtrate was evaporated again. The residue was extracted with boiling benzene and the insoluble fraction was again filtered off. The filtrate was evaporated and crystallisation of the residue from petroleum ether yielded 4.4 g of 5-fluoro-2-(4-(trifluoromethyl)phenylthio)benzoic acid with melting point 127-129.5 ^{0}C.

A mixture of 4.2 g of 5-fluoro-2-(4-(trifluoromethyl)-phenylthio)benzoic acid, 40 ml of benzene and 4.8 g of thionylchloride was refluxed for 1.5 h and processed in analogy to example 1/b, which yielded 3.9 g of oily 5-fluoro-2-(4-(trifluoromethyl)phenylthio)benzoyl chloride.

A solution of 3.9 g of 5-fluoro-2-(4-(trifluoromethyl)-phenylthio)benzoylchloride was dissolved in 30 ml of benzene and was mixed under intensive stirring over a period of 15 min with 10 ml of 40% aqueous dimethylamine and processed in analogy to example 1/c, which yielded 4.0 g of oily N,N-di-methyl-5-fluoro-2-(4-(trifluoromethyl)phenylthio)-benzamide.

1.0 g of sodium borohydride was added to a solution of 4.0 g of oily N,N-dimethyl-5-fluoro-2-(4-(trifluoromethyl)-phenylthio)benzamide in 30 ml of tetrahydrofuran and then 4.5 g of boron trifluoride etherate was added dropwise under nitrogen and under stirring over a period of 10 min. The mixture was processed in analogy to example 1/d to obtain the crude base (3.5 g). This was dissolved in ether and the solution was neutralised with a solution of 1.5 g of oxalic acid dihydrate in acetone. The precipitated crude N,N-dimethyl-5-fluoro-2-(4-(trifluoromethyl)phenylthio)benzylamine hydrogen oxalate recrystallised from ethanol to obtain 3.25 g of the pure salt with melting point 177.5-179.5 ^{0}C.

Example 23:

N,N-Dimethyl-2-(4-(methylthio)phenylthio)benzylamine.

a) A reaction of 12.4 g of 2-(4-(methylthio)phenylthio)-benzoic acid (Pelz K. et. al: Collect. Czech. Chem. Commun. 33, 1895 (1968)) in 100 ml of benzene with 11 ml of thionyl-chloride, carried out in analogy to example 1/b, yielded 13.0 g of crude 2-(4-(methylthio)phenylthio)benzoyl chloride as a yellowish oil.

b) A reaction of 13.0 g of crude 2-(4-(methylthio)phenyl-thio)benzoyl chloride in 80 ml of benzene with 40 ml of 40% aqueous dimethylamine, carried out in analogy to example 1/c, yielded 13.2 g of oily N,N-dimethyl-2-(4-(methylthio)-phenylthio)benzamide.

c) 3.0 g of sodium borohydride was added to a solution of 13.6 g of oily N,N-dimethyl-2-(4-(methylthio)phenylthio)-benzamide in 80 ml of tetrahydrofuran and then 12.0 g of boron trifluoride etherate was added dropwise under nitrogen and under stirring over a period of 30 min. The mixture was processed in analogy to example 1/d, which provided 14 g of the crude base. This was neutralised with a solution of hydrogen chloride in ether, and after crystallisation from a mixture of acetone and ethanol 8.3 g of N,N-dimethyl-2-(4-(methylthio)phenylthio)benzylamine hydrochloride was yielded, with melting point 141-144^{0}C.

Example 24:

N,N-Dimethyl-5-fluoro-2-(4-(methylthio)phenylthio)-benzylamine.

A reaction of 12.4 g of 5-fluoro-2-(4-(methylthio)phenylthio)benzoic acid (Kopicová Z. et. al: Collect. Czech. Chem. Commun. 40. 3519 (1975)), 90 ml of benzene and 16 g of thionylchloride, carried out in analogy to example 1/b and crystallisation from cyclohexane yielded 11.1 g of 5-fluoro-2-(4-(methylthio)phenylthio)benzoyl chloride with melting point 77-78^{0}C.

A reaction of 11.1 g of 5-fluoro-2-(4-(methylthio)phenylthio)benzoyl chloride in 60 ml of benzene with 20 ml of 40% aqueous dimethylamine, carried out in analogy to example 1/c, yielded oily N,N-dimethyl-5-fluoro-2-(4-(methylthio)-phenylthio)benzamide.

A reaction of 12.2 g of oily N,N-dimethyl-5-fluoro-2-(4-(methylthio)phenylthio)benzamide in 70 ml of tetrahydrofuran with 2.8 g of sodium borohydride and 12.5 g of boron trifluoride etherate, carried out in analogy to example 1/d, yielded 12.0 g of crude base. This was neutralised with a solution of hydrogen chloride in ether, which yielded

11.6 g of N,N-dimethyl-5-fluoro-2-(4-(methylthio)phenylthio)-benzylamine hydrochloride, which after crystallisation from a mixture of ethanol and ether melted at 160.5-162.5^{0}C.

Example 25:

N,N-Dimethyl-5-fluoro-2-(4-(methylsulfinyl)phenylthio)-benzylamine.

5 ml of 15% hydrogenperoxide was added to a solution of 2.6 g of N,N-dimethyl-5-fluoro-2-(4-(methylthio)phenylthio)-benzylamine hydrochloride (see example 24) in 12 ml of acetic acid and the mixture was left standing at room temperature for 4 days. After diluting with water, it was made alkaline by aqueous ammonium and extracted with ether. The extract was dried with potassium carbonate, filtered and the filtrate was evaporated, which yielded 2.3 g of the base of N,N-dimethyl-5-fluoro-2-(4-(methylsulfinyl)phenylthio)benzylamine base, which after crystallisation from a mixture of benzene and petroleum ether melted at 94-97^{0}C. Neutralisation of this base with a solution of hydrogen chloride in ether yielded the hydrochloride, which after crystallisation from a mixture of acetone, ethanol and ether melted at 221-223^{0}C.

Example 26:

N,N-Dimethyl-5-chloro-2-(4-(methylthio)phenylthio)-benzylamine.

5.0 g of 4-(methylthio)thiophenol, (Pelz K. et. al: Collect. Czech. Chem. Commun. 33, 1895 (1968)), 11.3 g of 5-chloro-2-iodobenzoic acid and 3.0 g of copper were step by step added to a solution of 6.8 g of potassium hydroxide in 120 ml of water and the mixture was refluxed for 8.5 h and

processed in analogy to example 1/a. The product was recrystallised from 400 ml of mixture of benzene and petroleum ether (1:1), filtered by suction and dried, yielding 8.9 g of 5-chloro-2-(4-(methylthio)phenylthiobenzoic acid (72%), which melted at 193-195^{0}C.

A reaction of 10.1 g of 5-chloro-2-(4-(methylthio)phenylthiobenzoic acid in 100 ml of toluene with 20 ml of thionylchloride (1 h under stirring at 80^{0}C) and processing in analogy to example 7/a yielded 9.8 g (95%) of 5-chloro-2-(4-(methylthio)phenylthiobenzoylchloride, which after crystallisation from a mixture of cyclohexane and petroleum ether melted at 78-81^{0}C.

9.4 g of 5-chloro-2-(4-(methylthio)phenylthionbenzoyl chloride in 50 ml of toluene reacted under intensive stirring and cooling with cold water with 30 ml of 40% aqueous dimethylamine. The mixture was stirred at room temperature for a further 2 h, the toluene phase was separated, washed with water and evaporated *in vacuo*. The residue was dissolved in chloroform and was purified by filtration on a silica gel column, which was eluted with chloroform. The filtrate evaporated *in vacuo* again, which yielded 7.55 g of oily N,N-dimethyl-5-chloro-2-(4-(methylthio)phenylthio)benzamide.

A reaction of 7.41 g of oily N,N-dimethyl-5-chloro-2-(4-(methylthio)phenylthio)benzamide in 60 ml of tetrahydrofuran with 3.0 g of sodium borohydride and 10 ml of boron trifluoride etherate, carried out in analogy to example 1/d, yielded the crude base, which was neutralised with a solution of 3.0 g of oxalic acid dihydrate in 80 ml of ethanol. After 16 h of standing, the precipitated product was filtered by suction, washed with ethanol and dried, which yielded 5.05 g (53%) of N,N-dimethyl-5-chloro-2-(4-(methylthio)phenylthio)-benzylamine hydrogen oxalate, m.p. 131-134^{0}C.

Example 27:

N,N-Dimethyl-2-(4-(fluoro-3-methoxyphenylthio)benzylamine.

A mixture of 18.5 g of thiosalicylic acid, 150 ml of dimethylformamide, 33.15 g of potassium carbonate, 24.6 g of 5-bromo-2-fluoroanisole (EP 175,452; JP 61/27,768; Chem. Abstr. 105, 42658 (1986)) and 2.2 g of copper was refluxed for 12 h. After cooling, the reaction mixture was diluted with 1.1 l of water, filtered and washed with benzene. The water phase was acidified with hydrochloric acid, the precipitated crude 2-(4-(fluoro-3-methoxyphenylthio)benzoic acid (20.6 g) was filtered by suction and after crystallisation from ethanol melted at 222-224^{0}C.

A reaction of 8.82 g of 2-(4-(fluoro-3-methoxyphenylthio)-benzoic acid in 70 ml of benzene with 12.3 g of thionylchloride, carried out in analogy to example 1/b, yielded 8.6 g (91%) of 2-(4-(fluoro-3-methoxyphenylthio)benzoylchloride, which after crystallisation from a mixture of benzene and cyclohexane melted at 113-114.5^{0}C.

A reaction of 8.45 g of 2-(4-(fluoro-3-methoxyphenylthio)-benzoyl chloride in 60 ml of benzene with 13 ml of 40% aqueous dimethylamine, carried out in analogy to example 1/c, yielded 7.3 g of crystalline N,N-dimethyl-2-(4-fluoro-3-methoxyphenylthio)benzamide, which after recrystallisation from methanol melted at 97-98,5^{0}C.

1.75 g of sodium borohydride was added to a solution of 7.0 g of N,N-dimethyl-2-(4-(fluoro-3-methoxyphenylthio)benzamide in 45 ml of tetrahydrofuran and then 6.8 g of boron trifluoride etherate was added dropwise under nitrogen and under stirring. The mixture was processed in analogy to example 6/d, except for the use of a solution of hydrogen chloride in ether for neutralisation. The procedure yielded 6.52 g of N,N-dimethyl-2-(4-(fluoro-3-methoxyphenylthio)-benzylamine hydrochloride, which after recrystallisation from a mixture of acetone and ether melted at 146-148^{0}C.

Example 28:

N,N-Dimethyl-2-(4-fluoro-3-hydroxyphenylthio)benzylamine.

A solution of 7.0 g of N,N-dimethyl-2-(4-fluoro-3-methoxyphenylthio)benzylamine hydrochloride (see example 27) in 50 ml of 46% hydrobromic acid was heated up to 120^{0}C under stirring for 8 h. After cooling, the mixture was diluted with 100 ml of water, its pH was adjusted up to 8 using 20% solution of sodium hydroxide, and the mixture was extracted with chloroform. The extract was filtered over a 100 g silica gel column, which was eluted with chloroform. The filtrate was evaporated, which yielded 4.71 g of the base of oily N,N-dimethyl-2-(4-(fluoro-3-hydroxyphenylthio)benzylamine. Its neutralisation with the corresponding acids and crystallisation from benzene, or a mixture of ethanol and ether, respectively, yielded the hydrochloride with melting point 172-175^{0}C, and hydrogen maleate with melting point 148-150^{0}C.

Example 29:

N,N-Dimethyl-2-(4-chloro-3-methoxyphenylthio)benzylamine.

A reaction of 4.7 g of 2-(4-chloro-3-methoxyphenylthio)-benzoic acid (Červená I. et. al: Collect. Czech. Chem. Commun. 42, 1705 (1977)) in 35 ml of benzene and 3.8 ml of thionylchloride, carried out in analogy to example 1/b, yielded 4.1 g (82%) of crystalline 2-(4-chloro-3-methoxyphenylthio)benzoylchloride, which after recrystallisation from cyclohexane melted at 117-118.5^{0}C.

A solution of 3.6 g of 2-(4-chloro-3-methoxyphenylthio)-benzoyl chloride in 45 ml of toluene was under stirring and external cooling by water and ice saturated with gaseous dimethylamine for 1 h. The mixture was stirred for a further 2 h and evaporated *in vacuo*. The oily residue was mixed with a small amount of a mixture of cyclohexane and hexane (1:1) and crystallised. The product's filtration by suction yielded 3.0 g of N,N-dimethyl-2-(4-chloro-3-methoxyphenylthio)-

benzamide, which after recrystallisation from a mixture of hexane and cyclohexane melted at 84-86^{0}C.

0.7 g of sodium borohydride was added to a solution of 2.65 g of N,N-dimethyl-2-(4-chloro-3-methoxyphenylthio)benzamide in 20 ml of tetrahydrofuran and then 2.26 g of boron trifluoride etherate was added dropwise under nitrogen and under stirring. The mixture was processed in analogy to example 1/d, which yielded 2.35 g (92%) of the oily crude base. Using hydrogen chloride in ether yielded N,N-dimethyl-2-(4-chloro-3-methoxyphenylthio)benzylamine hydrochloride, which after crystallisation from 2-propanol melted at 162-164^{0}C.

Example 30:

N,N-Dimethyl-2-(4-trifluoromethyl)-2-nitrophenylthio)-benzylamine.

22.8 g of 2-methylthiophenol, 41.4 g of 2-chloro-5-(trifluoromethyl)nitrobenzene and 2.0 g of copper were added to a solution of 30.6 g of potassium hydroxide in 325 ml of water. The mixture was refluxed under stirring for 9 h, and after cooling extracted with toluene. The extract was dried with magnesium sulfate, filtered and evaporated, which yielded 50 g of the oily crude 2-(4-trifluoromethyl)-2-nitrophenylthio)toluene of orange colour. After cooling to 0^{0}C, the product crystallised and after recrystallisation from hexane melted at 55-56^{0}C.

37 g of N-bromosuccinimide and 0.5 g of 2,2 -azobis(2-methylpropionitrile) were added to a solution of 54.2 g of 2-(4-trifluoromethyl)-2-nitrophenylthio)toluene in 400 ml of tetrachloromethane and the mixture was refluxed under stirring for 4 h. After cooling the precipitated solid compound was filtered off and washed with tetrachloromethane, which yielded 470 ml of filtrate containing 2-(4-trifluoro-

methyl)-2-nitrophenylthio)benzylbromide. For its characterisation this was isolated from a part of the filtrate as follows: 45 ml of the filtrate was evaporated *in vacuo*, then chromatographed on a 100 g silica gel column and the column was eluted by petroleum ether, then cyclohexane and 5% toluene in cyclohexane. After isolation and crystallisation from a mixture of petroleum ether and cyclohexane, the product melted at 77-79^{0}C.

The filtrate (302 ml) containing 2-(4-trifluoromethyl)-2-nitrophenylthio)benzylbromide was cooled to -10^{0}C and a solution of excess dimethylamine in tetrachloromethane was added little by little under stirring. The mixture was stirred at room temperature for 3 h and the precipitated dimethylamine hydrobromide was filtered off. The filtrate was washed with water, dried with magnesium sulfate and evaporated, which yielded 40 g of the crude oily base of N,N-dimethyl-2-(4-trifluoromethyl)-2-nitrophenylthio)benzylamine, which crystallised on standing and after recrystallisation from hexane melted at 59-60^{0}C. Its neutralisation and crystallisation from a mixture of ethanol and ether, or aqueous ethanol, respectively, yielded the following salts: the hydrobromide melting at 193-195^{0}C and hydrogen oxalate melting at 218-219^{0}C.

Example 31:

N,N-Dimethyl-2-(2-aminophenylthio)benzylamine.

a) A solution of 4.9 g of 2-(2-aminophenylthio)benzoic acid (Mayer F.: Ber. Dtsch. Chem. Ges. 42, 3046 (1909)) in 50 ml of tetrahydrofuran was added dropwise under stirring over a period of 30 min to a solution of 1.7 g of lithium aluminium hydride in 70 ml of tetrahydrofuran and after an exothermic reaction the mixture was refluxed for 5 h. After 16 h of standing, the mixture was decomposed under stirring

by adding dropwise 6.7 ml of 4% solution of sodium hydroxide. The precipitated solid was filtered off and the filtrate was dried with magnesium sulfate and evaporated *in vacuo*, which yielded 4.3 g (93%) of 2-(2-aminophenylthio)benzyl alcohol. This crystallised on standing and after recrystallisation from cyclohexane melted at 107-108.5 ^{0}C. It provides hydrochloride, which after recrystallisation from a mixture of 2-propanol and ethanol melted at 143-147 ^{0}C.

b) 2.6 g of 2-(2-aminophenylthio)benzyl alcohol was slowly mixed at room temperature with 2.7 g of thionylchloride and the mixture was left standing at room temperature for 1 h. Then it was diluted with 20 ml of benzene and all volatile constituents absolutely evaporated off *in vacuo*. The residue was 2.7 g of oily crude 2-(2-aminophenylthio)benzyl chloride.

c) A solution of 1.4 g of dimethylamine in 3 ml of toluene was added to a solution of 1.15 g of 2-(2-aminophenylthio)-benzyl chloride in 8 ml of toluene and the mixture was under external cooling by water and ice stirred for 1.5 h. After 16 h of standing, the precipitated dimethylamine hydrochloride was filtered off and the filtrate was evaporated, which yielded 1.1 g (92%) of the base as a brown oil. Neutralisation of 1.0 g of this base with 0.7 g oxalic acid dihydrate in 5 ml of heated ethanol yielded crystalline N,N-dimethyl-2-(2-aminophenylthio)benzylamine hydrogen oxalate, which after crystallisation from aqueous methanol melted at 182-186 ^{0}C.

Example 32:

N,N-Dimethyl-2-(3-aminophenylthio)benzylamine.

7.15 g of crude 3-aminothiophenol (Zincke T., Müller J.: Ber. Dtsch. Chem. Ges. 46, 775 (1913)) was added to a solution of 8.9 g of potassium hydroxide in 80 ml of water and

after 20 min of stirring at 50^{0}C also 14.1 g of 2-iodobenzoic acid and 0.2 g of copper as catalyst were added. The mixture was refluxed for 12 h. After adding of filtration charcoal, the mixture was filtered hot, and the partially cooled filtrate was acidified with diluted hydrochloric acid (1:1). The product was filtered by suction and crystallised from aqueous 2-propanol, which yielded 7.7 g of 2-(3-aminophenylthio)benzoic acid with melting point 160-163^{0}C.

3.66 g of absolutely dry 2-(3-aminophenylthio)benzoic acid was slowly added to a solution of 3.0 g of lithium aluminium hydride in 100 ml of tetrahydrofuran. The mixture was stirred at room temperature for 30 min, then refluxed for 3.5 h and processed in analogy to example 31/a, which yielded 3.1 g (89%) of crystalline 2-(3-aminophenylthio)benzyl alcohol, which after crystallisation from cyclohexane melted at 69-71^{0}C.

Under cooling by ice and water 3.0 g of 2-(3-aminophenylthio)benzyl alcohol and 2.5 ml of thionylchloride were slowly mixed and the mixture was left standing at room temperature for 1 h. The excess thionylchloride evaporated off *in vacuo* and the gained crude 2-(3-aminophenylthio)benzyl chloride hydrochloride was suspended in 20 ml of toluene. 4.5 ml of dimethylamine in 10 ml of toluene was added dropwise under stirring and under external cooling by ice and water. The mixture was left standing at room temperature for 2 h, and was then stirred for a further 2 h. The precipitated dimethylamine hydrochloride was filtered off by suction and the filtrate was evaporated *in vacuo*. The residue was 3.0 g of the oily crude base, which was dissolved in a small amount of ethanol and neutralised with a solution of 2.8 g of the oxalic acid dihydrate in ethanol. On standing there precipitated 3.4 g of N,N-dimethyl-2-(3-aminophenylthio)-benzylamine bis(hydrogen oxalate), which after crystallisation from methanol melted at 161-162^{0}C.

Example 33:

N,N-Dimethyl-2-(4-aminophenylthio)benzylamine.

A mixture of 3.7 g of 2-(4-aminophenylthio)benzyl alcohol (Adlerová E. et. al: Collect. Czech. Chem. Commun. 33, 2666 (1968)) and 3.8 g of thionylchloride was processed in analogy to example 31/b. The procedure yielded 3.8 g of crude 2-(4-aminophenylthio)benzyl chloride hydrochloride.

A solution of 4.6 ml of dimethylamine in 10 ml of toluene was added dropwise under stirring to a suspension of 3.8 g of crude 2-(4-aminophenylthio)benzylchloride hydrochloride in 25 ml of toluene and the mixture was processed in analogy to example 31/c, which yielded 3.8 g of the oily base. This was dissolved in 10 ml of ethanol and neutralised with a solution of 3.7 g of oxalic acid dihydrate in 15 ml of ethanol. After 16 h of standing in cold, 3.2 g of N,N-dimethyl-2-(4-aminophenylthio)benzylamine bis(hydrogen oxalate) crystallised, which after subsequent crystallisation from methanol melted at 164-166^{0}C.

Example 34:

N,N-Dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)-benzylamine.

9.4 g of hydrazinehydrate, 1.3 g of filtration charcoal and a solution of 9.4 g of ferric chloride hexahydrate in 15 ml of ethanol were added under stirring to a suspension of 26.0 g of 2-(4-(trifluoromethyl)-2-nitrophenylthio)benzoic acid (GB 925,539). The mixture was refluxed for 8.5 h. After 16 h of standing, ethanol evaporated off *in vacuo*. A solution of 8.6 g of sodium hydroxide in 45 ml of water was added to the residue, the mixture was diluted with 115 ml of water and 1.3 g of filtration charcoal was added. After hea-

ting up to 90^0C, the mixture was filtered, the filtrate was cooled to 15^0C and under stirring was acidified with 22 g of acetic acid added dropwise. The precipitated product was filtered by suction, washed with water and dried, which yielded 19.9 g (81%) of 2-(2-amino(-4-(trifluoromethyl)-phenylthio)benzoic acid, which after crystallisation from benzene melted at 188-190^0C.

A solution of 37.6 g of 2-(2-amino(-4-(trifluoromethyl)-phenylthio)benzoic acid in 350 ml of tetrahydrofuran was under stirring slowly added dropwise to a solution of 11.6 g of lithium aluminium hydride in 400 ml of tetrahydrofuran and the mixture was refluxed for 5 h. After cooling, the mixture was decomposed by slow adding dropwise of 4% solution of sodium hydroxide (47 ml) under external cooling. Then the mixture was stirred at room temperature for 1.5 h and the precipitated compound was filtered by suction and washed with ether. The filtrate was dried with magnesium sulfate and evaporated *in vacuo*. The oily residue crystallised on standing and recrystallisation from cyclohexane yielded 21.8 g (61%) of 2-(2-amino-4-(trifluoromethyl)phenyl-thio)benzyl alcohol with melting point 88-89^0C.

When working with bigger charges, the reduction of the acid into alcohol is more suitably carried out in the following way: 323 g of 70% solution (toluen) of sodium dihydridobis(2-methoxyethoxo)aluminate $(NaAlH_2(OCH_2CH_2OCH_3)_2$ in 300 ml of toluene was under stirring over a period of 75 min added dropwise to a solution of 125 g of 2-(2-amino-4-(trifluoromethyl)phenylthio)benzoic acid in 2 l of toluene and the mixture was stirred at room temperature for 4 h. Under external cooling and under stirring then it was decomposed by adding 2000 ml of 10% solution of sodium hydroxide. The toluene phase was separated, the aqueous phase was extracted with toluene and the toluene solutions were put together, dried with magnesium sulfate and after filtration the toluene evaporated off *in vacuo*. The residue was 101 g

(92%) of crude 2-(2-amino-4-(trifluoromethyl)phenylthio)-benzyl alcohol, which after crystallisation from cyclohexane melted at 88-89^{0}C and was identical to the product of the previous reduction.

59.8 g of 2-(2-amino-4-(trifluoromethyl)phenylthio)benzyl alcohol was added under stirring at 5-8^{0}C over a period of 1 h to 29.2 ml of thionylchloride and the mixture was then stirred at room temperature for 2 h. The excess thionylchloride was absolutely evaporated off *in vacuo* and the solid product was stirred up with cyclohexane and filtered by suction, which yielded 70.8 g (100%) of 2-(2-amino-4-(trifluoromethyl)phenylthio)benzyl chloride hydrochloride, which melted at 89-93^{0}C.

A solution of 40 ml of dimethylamine in 40 ml of toluene was added dropwise under stirring and under external cooling to a suspension of 70.8 g of 2-(2-amino-4-(trifluoromethyl)-phenylthio)benzyl chloride in 100 ml of toluene. The mixture was stirred at room temperature for a further 1 h and was processed in analogy to example 31/c, which yielded 57.4 g (88%) of the oily crude base of N,N-dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)benzylamine, which after crystallisation melted at 58-59^{0}C. Its neutralisation with hydrogenchloride in a mixture of ethanol and ether yielded dihydrochloride, which crystallised from a mixture of ethanol and ethylacetate as monohydrate with melting point 180-183^0. Neutralisation of the base with oxalic acid dihydrate in hot ethanol and its subsequent cooling yielded the oxalate, which after crystallisation from aqueous ethanol melted at 213-216^{0}C.

Example 35:

N,N-Dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzylamine.

A solution of 40.0 g of 2-(2-amino-4-(trifluoromethyl)-

phenylthio)-5-fluorobenzoic acid (see example 22) in 200 ml of tetrahydrofuran was added dropwise under stirring over a period of 15 min to a solution of 13.2 g of lithium aluminium hydride in 100 ml of tetrahydrofuran and the mixture was refluxed under stirring for 4 h. After 16 h of standing, the mixture decomposed by adding dropwise of 10% solution of sodium hydroxide (40 ml) under stirring. After 2.5 h of stirring, the precipitated compound was filtered off by suction, the filtrate was dried with potassium carbonate and was evaporated. The residue was 41 g of crude 2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzylalcohol to which 40 ml of thionylchloride was added dropwise under cooling with ice and under stirring. The mixture was stirred at room temperature for 2 h and left standing for 16 h. The excess thionylchloride evaporated off *in vacuo*. The residue was crude 2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzyl chloride hydrochloride. This was dissolved in 50 ml of benzene and a solution of 40 g of dimethylamine in 50 ml of benzene was added dropwise under stirring and under cooling. The mixture was stirred for 6 h and after 48 h of standing the precipitated dimethylamine hydrochloride was filtered off by suction. The filtrate was evaporated *in vacuo* and the residue was chromatographed on a 150 g silica gel column. Elution with chloroform yielded 23.5 g of the oily base, which with hydrogen chloride in ether provided N,N-dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)-5-fluorobenzylamine hydrochloride hemihydrate. This crystallised from a mixture of ethanol and ether as a crystalline modification melting at 181-184^{0}C, and from a mixture of 2-propanol and ethylacetate as another crystalline modification melting at 124-128^{0}C.

Example 36:

N,N-Dimethyl-2-(4-amino-2-(trifluoromethyl)phenylthio)-benzylamine

0.93 g of thiosalicylic acid and 1.6 g of 2-bromo-5-nitrobenzotrifluoride (Filler R., Novar H.: J. Org. Chem. 26, 2707 (1961)) were added to a solution of 0.48 g of sodium hydroxide in 25 ml of ethanol and the mixture was refluxed under stirring for 2.5 h. The ethanol evaporated off *in vacuo* and the residue was dissolved in 25 ml of hot water. After cooling, the mixture was acidified under stirring with 2.5 ml of 3M hydrochloric acid. Filtration, washing with water and drying yielded 1.85 g (92%) of crude 2-(2-(trifluoromethyl)-4-nitrophenylthio)benzoic acid, which after crystallisation from aqueous methanol melted at 150-152^{0}C.

0.2 g of filtration charcoal and a solution of 0.1 g of ferric chloride hexahydrate in 5 ml of ethanol were added to a solution of 2.92 g 2-(2-(trifluoromethyl)-4-nitrophenylthio)benzoic acid in 15 ml of 96% ethanol. The mixture was refluxed for 7.5 h, the ethanol evaporated off *in vacuo* and the residue was dissolved at 60^{0}C in 1M solution of sodium hydroxide. The solution was filtered using filtration charcoal, cooled and made slightly acid with acetic acid. The precipitate was filtered by suction, washed with water and dried, which yielded 1.26 g (47%) of 2-(4-amino-2-(trifluoromethyl)phenylthio)benzoic acid, which after crystallisation from a mixture of benzene and petroleum ether melted at 210-214^{0}C.

A solution of 3.13 g of 2-(4-amino-2-(trifluoromethyl)-phenylthio)benzoic acid in 30 ml of ether was under stirring slowly added dropwise to a solution of 1.52 g of lithium aluminium hydride in a mixture of 15 ml of ether and 15 ml of tetrahydrofuran and was refluxed for 1.5 h. After 16 h of standing, it decomposed by adding dropwise of 5% sodium hydroxide (6 ml) under stirring. The precipitated compound was filtered off by suction and the filtrate was evaporated *in vacuo*. The residue was chromatographed on a 25 g silica gel column, which was eluted with benzene. The procedure yielded 2.7 g of 2-(4-amino-2-(trifluoromethyl)phenylthio)-

benzyl alcohol, which provided crystalline hydrochloride. This after crystallisation from a mixture of ethanol and ether melted at 160-162^{0}C.

A solution of hydrogen chloride in ether (2 ml containing 5.5 mmol of hydrogen chloride) was added to a solution of 1.61 g of 2-(4-amino-2-(trifluoromethyl)phenylthio)benzyl alcohol in 5.5 ml of benzene and then 5.2 ml of thionylchloride was added dropwise under stirring over a period of 20 min. The reaction mixture was stirred at 24^{0}C for 1.5 h and the volatile constituents absolutely evaporated off *in vacuo*. The residue was 1.7 g (100%) of 2-(4-amino-2-trifluoromethyl)phenylthio)benzyl chloride hydrochloride, which was dissolved in 15 ml of toluene and then a solution of dimethylamine (5x in excess) in 10 ml of toluene was added. The mixture was stirred at room temperature for 1 h and after 16 h of standing it was washed with water. The toluene solution was dried with potassium carbonate and was evaporated *in vacuo*. The residue was 1.65 g of the base as an oily liquid. Neutralisation with oxalic acid dihydrate in ethanol hot followed by cooling yielded 1.53 g (88%) of N,N-dimethyl-2-(4-amino-2-(trifluoromethyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from 2-propanol melted at 161-163.5^{0}C.

Example 37:

N,N-Dimethyl-2-(3-(hydroxymethyl)phenylthio)benzylamine.

A mixture of 200 ml of dimethylformamide, 24 g of N,N-dimethyl-2-iodobenzamide (Cohen T. et. al: Tetrahedron Lett. 40, 3555 (1974)), 13.7 g of 3-mercaptobenzoic acid, 25 g of potassium carbonate and 1 g of copper was refluxed in the bath heated up to 150^{0}C under stirring for 9 h. Dimethylformamide was distilled off *in vacuo*, the residue was diluted with 200 ml of water, the resulting liquid was filtered and

the filtrate was acidified with diluted hydrochloric acid (1:1). After 30 min of standing, the precipitate was filtered by suction, dissolved in hot ethanol, the insoluble fraction was filtered off and the filtrate was evaporated. The residue was chromatographed on a 150 g silica gel column, which was gradually eluted with benzene, chloroform, ethylacetate and ethanol. The ethylacetate eluates were evaporated, which yielded 12.4 g of homogenous oily N,N-dimethyl-2-(3-(carboxy phenylthio)benzamide.

12.4 g of oily N,N-dimethyl-2-(3-(carboxyphenylthio)benzamide in 100 ml of tetrahydrofuran, 4.8 g of sodium borohydride and 18.8 g of boron trifluoride etherate were processed in analogy to example 23/c, which yielded 9.8 g of oily base. Its neutralisation with oxalic acid dihydrate in acetone yielded crystalline N,N-dimethyl-2-(3-(hydroxymethyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from a mixture of acetone, ethanol and ether melted at 111.5-113^{0}C.

Example 38:

N,N-Dimethyl-2-(4-(hydroxymethyl)phenylthio)benzylamine.

3.98 g of crude N,N-dimethyl-2-mercaptobenzamide (Schindlbauer H.: Monatsh. Chem. 99, 1799 (1968)), 3.04 g potassium carbonate and 2.63 g of 4-chlorobenzaldehyde were added under stirring to 40 ml of dimethylformamide and the mixture was refluxed for 8 h up to the boiling point. It was diluted with 200 ml of water and extracted with a mixture of ether and ethylacetate. After filtration with filtration charcoal, the extract was dried with potassium carbonate and evaporated *in vacuo*. 5.06 g (95%) of oily crude N,N-dimethyl-2-(4-formylphenylthio)benzamide was obtained, which was purified by chromatography on a silica gel column eluted with a mixture of ethylacetate and benzene.

2.27 g of sodium borohydride was added to a solution of 5.14 g of N,N-dimethyl-2-(4-formylphenylthio)benzamide in 30 ml of tetrahydrofuran and after 16 h of standing, 7.67 g of boron trifluoride etherate was added dropwise under stirring in nitrogen atmosphere at 17-24^{0}C over a period of 0.5 h. After 1 h of stirring at room temperature, the mixture was refluxed for 8 h. After 16 h of standing at room temperature, the mixture was diluted with 10 ml of tetrahydrofuran and then was acidified under stirring at 20-30^{0}C by adding dropwise of 60 ml of 6M HCl. The mixture was refluxed for a further 3.5 h. After cooling it was made alkaline with 10M solution of sodium hydroxide and extracted with chloroform. The extract was dried with potassium carbonate and evaporated *in vacuo*. The residue was 4.42 g (90%) of the crude base, which was purified by crystallisation on a silica gel column gradually eluted with a mixture of chloroform and ethylacetate, chloroform and a mixture of methanol and chloroform saturated with ammonium at last. The residue of the chloroform eluate was an oily base whose neutralisation with oxalic acid dihydrate in acetone yielded crystalline N,N-dimethyl-2-(4-(hydroxymethyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from a mixture of acetone, ethanol and ether melted at 96-98^{0}C.

Example 39:

N,N-Dimethyl-2-(4-(hydroxymethyl)phenylthio)benzylamine.

This is an alternative method of preparation of the compound according to example 38.

A mixture of 25 ml of dimethylformamide, 4.15 g of 4-mercaptobenzyl alcohol (Pelz et al.: Collect. Czech. Chem. Commun. 33, 1895 (1968)), 3.73 g 2-chlorobenzaldehyde, 3.95 g of potassium carbonate and 0.16 g of copper, as a catalyst, was refluxed under stirring at 98-109^{0}C for 8 h.

After 16 h of standing, the insoluble fractions were filtered off and still on the filter were washed with ethanol. The filtrate was filtered with 1 g of filtration charcoal and evaporated *in vacuo*. The residue was divided into 10 ml of water and 3 x 3 ml of ether. The ether phases were put together and were evaporated. The residue reacted with a solution of 10.4 g of potassium pyrosulfite in 26 ml of water. The precipitated "bisulfite adduct" was filtered off by suction, decomposed by 10 ml of 3M sulfuric acid and the free aldehyde was extracted with ether and chloroform. 4.42 g of oily 2-(4-(hydroxymethyl)phenylthio)benzaldehyde was obtained from the extract.

For its characterisation this aldehyde can be converted to crystalline 2,4-dinitrophenylhydrazon in a familiar way, which after crystallisation from a mixture of ethylacetate and ethanol melted at 216-222^{0}C.

A mixture of 3.82 g of 2-(4-(hydroxymethyl)phenylthio)-benzaldehyde, 8 ml of dimethyformamide (7.5 g) and 4.6 g of formic acid was refluxed under stirring for 7.5 h (bath temperature was 160-170^{0}C). After cooling, the mixture was acidified with an addition of 30 ml of 5% hydrochloric acid and the fractions which were not basic were removed by washing with ether. The aqueous solution was filtered with filtration charcoal, the filtrate was made alkaline with 15 ml of 5M solution of sodium hydroxide and the product was extracted with dichloroethane. The extract was dried with potassium carbonate and evaporated *in vacuo*. The residue was 3.96 g (93%) of the oily base, whose neutralisation with oxalic acid dihydrate in ethanol yielded crystalline N,N-dimethyl-2-(4-(hydroxymethyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from ethanol melted at 96-98^{0}C and was identical to the compound prepared as described in example 38.

Example 40:

N,N-Dimethyl-2-(2-(dimethylaminomethyl)phenylthio)-benzylamine.

a) 12.2 ml of thionylchloride in 20 ml of benzene was added dropwise under stirring to a solution of 4.11 g of diphenylsulfido-2-2 -dicarboxylic acid (Mayer F.: Ber. Dtsch. Chem. Ges. 43, 588 (1910)) in 40 ml of benzene and the mixture was refluxed for 4 h. After evaporating and cooling, the solid residue was mixed with a small amount of cyclohexane and isolated by filtration, which yielded 4.28 g (92%) of crystalline diphenylsulfide-2-2 -dicarboxylic acid dichloride, which after crystallisation from cyclohexane melted at 80-83^{0}C.

b) A solution of 3.60 g of diphenylsulfide-2-2 -dicarboxylic acid dichloride in 40 ml of benzene was mixed with 17 ml of 40% aqueous dimethylamine over a period of 1 h under intensive stirring and external cooling with ice and water. The mixture was stirred at room temperature for 3 h and then was processed in analogy to example 1/c. The procedure yielded 3.52 g (93%) of oily N,N-dimethyl-2-(2-(dimethylaminocarbonyl)phenylthio)benzamide, which crystallised on standing (m.p. 95-102^{0}C).

c) A reaction of oily N,N-dimethyl-2-(2-(dimethylaminocarbonyl)phenylthio)benzamide in 40 ml of tetrahydrofuran, 1.84 g of sodium borohydride and 6.4 g of boron trifluoride etherate, in analogy to example 1/d, yielded 3.08 g (96%) of the oily base. This was dissolved in 50 ml of ether and the solution was acidified with 8 ml of ether containing 1.0 g of hydrogen chloride. The precipitated crude N,N-dimethyl-2-(2-(dimethylaminomethyl)phenylthio)benzylamine dihydrochloride crystallised from 2-propanol containing a small amount of water as hemihydrate (m.p. 205-206^{0}C).

Example 41:

N,N-Dimethyl-2-(3-(dimethylaminomethyl)phenylthio)-benzylamine.

a) 6.16 g of thiosalicylic acid, 9.92 g of 3-iodobenzoic acid and 0.66 g of copper were gradually added to a solution of 9.0 g of potassium hydroxide in 90 ml of water. The mixture was refluxed for 6 h under stirring. After cooling, pH of the mixture was adjusted up to 9 by addition of 5 ml of diluted hydrochloric acid (1:1). Filtration charcoal was added and the mixture was stirred at 80^0C for 10 min, then filtered hot and after cooling the filtrate was acidified with hydrochloric acid up to pH=1. After dilution with 200 ml of water, the fine precipitate was filtered off by suction, washed with water and dried to obtain 10.62 g (97%) of crude diphenylsulfide-2,3 -dicarboxylic acid, which after crystallisation from aqueous ethanol melted at $308-310^0C$.

b) A reaction of 9.68 g of crude diphenylsulfide-2,3 -dicarboxylic acid in 110 ml of benzene with 46 g of thionylchloride (4 h of refluxing) in analogy to example 40/a, yielded 9.83 g (90%) of crude diphenylsulfide-2,3 -dicarboxylic acid dichloride, which after crystallisation from cyclohexane melted at $112-113^0C$.

c) A reaction of 8.8 g of diphenylsulfide-2,3 -dicarboxylic acid dichloride in 160 ml of benzene with 36.6 g of 40% aqueous dimethylamine in analogy to example 40/b, yielded 9.28 g (100%) of oily N,N-dimethyl-2-(3-(dimethylaminocarbonyl)phenylthio)benzamide, which crystallised on standing and after recrystallisation from ethanol melted at $129-130^0C$.

d) In analogy to example 40/c, a reaction of 9.28 g of N,N-dimethyl-2-(3-(dimethylaminocarbonyl)phenylthio)benzamide with 4.88 g of sodium borohydride and 15.5 ml of boron trifluoride etherate in 80 ml of tetrahydrofuran yielded 6.33 g (75%) of the oily base. This was converted into N,N-dimethyl-

2-(3-(dimethylaminomethyl)-phenylthio)benzylamine dihydrochloride, which crystallised from 2-propanol as the solvate containing 1/2 of molecule of this solvent (m.p. 138-141^0).

Example 42:

N,N-Dimethyl-2-(4-(dimethylaminomethyl)phenylthio)-benzylamine.

In analogy to example 41/a, a reaction of 4.5 g of potassium hydroxide in 45 ml of water, 3.08 g of thiosalicylic acid, 4.96 g of 4-iodobenzoic acid and 0.35 g of copper yielded 4.61 g (84%) of diphenylsulfide-2,4 -dicarboxylic acid, which after crystallisation from 50% aqueous ethanol melted at 234-236^{0}C.

A reaction of 4.11 g of diphenylsulfide-2,4 -dicarboxylic acid in 50 ml of benzene with 13.2 g of thionylchloride (2.5 h of refluxing) in analogy to example 40/a, yielded 4.31 g (92%) of solid diphenylsulfide-2,4 -dicarboxylic acid dichloride, which after crystallisation from cyclohexane melted at 104-106^{0}C.

A reaction of 4.3 g of diphenylsulfide-2,4 -dicarboxylic acid dichloride in 25 ml of benzene with 12.5 g of 40% aqueous dimethylamine in analogy to example 40/b, yielded 3.6 g (79%) of oily N,N-dimethyl-2-(4-(dimethylaminocarbonyl)-phenylthio)benzamide.

In analogy to example 40/c, a reaction of 3.6 g of N,N-dimethyl-2-(4-(dimethylaminocarbonyl)phenylthio)benzamide with 1.8 g of sodium borohydride and 6.4 g of boron trifluoride etherate in 40 ml of tetrahydrofuran yielded 3.3 g (100%) of the oily base. This was converted to crystalline N,N-dimethyl-2-(4-(dimethylaminomethyl)phenylthio)benzylamine dihydrochloride, which crystallised from 2-propanol (m.p. 233-235^{0}C).

Example 43:

N,N-Dimethyl-2-(2-carboxyphenylthio)benzylamine.

a) A mixture of 30 ml of dimethylformamide, 7.7 g of thiosalicylic acid, 7.0 g of 2-chlorobenzaldehyde, 14 g of potassium carbonate and 1.2 g of copper(I) chloride was heated up to 100^0C under stirring in 5 min and then stirred at $110-120^0C$ for 6 h. After 16 h of standing, the mixture was diluted with 220 ml of water at 60^0C and the resulting cloudy liquid was filtered with 1 g of filtration charcoal. After cooling, the filtrate was acidified with 5M HCl under stirring. The precipitate was filtered off by suction, washed with water and dried, which yielded 9.11 g of crude 2-(2-carboxyphenylthio)benzaldehyde with melting point $167-169^0C$.

b) A mixture of 5.1 g of 2-(2-carboxyphenylthio)benzaldehyde, 7.3 g of dimethylformamide and 4.5 g of formic acid was refluxed under stirring up to $110-120^0C$ for 15 h. After cooling, the mixture was acidified with a solution of 6 ml of hydrochloric acid in 60 ml of water and the resulting liquid was washed with toluene. After filtration, the aqueous solution was evaporated to dryness *in vacuo*. The residue was crystallised from a mixture of 2-propanol and ethylacetate, which yielded 6.0 g of crystalline N,N-dimethyl-2-(2-carboxyphenylthio)benzylamine hydrochloride monohydrate with melting point $96-99^0C$.

Example 44:

N,N-Dimethyl-2-(4-carboxyphenylthio)benzylamine.

In analogy to example 43/a - except for the use of 4-mercaptobenzoic acid instead of thiosalicylic acid (the same amount), 10.6 g (82%) of 2-(4-carboxyphenylthio)benz-

aldehyde with melting point 178-181^{0}C, which crystallised from 80% aqueous ethanol or toluene.

In analogy to example 43/b, a reaction of 5.5 g of dimethylformamide, 3.88 g of 2-(4-carboxyphenylthio)benzaldehyde and 3.5 g of formic acid yielded 3.7 g (76%) of N,N-dimethyl-2-(4-carboxyphenylthio)benzylamine hydrochloride, which after crystallisation from a mixture of ethanol and ether melted at 209-211^{0}C.

Example 45:

N,N-Dimethyl-2-(2-(ethoxycarbonyl)phenylthio)benzylamine.

6.4 g of N,N-dimethyl-2-(2-carboxyphenylthio)benzylamine hydrochloride monohydrate (see example 43) was dried at 80^{0}C *in vacuo*. The anhydrous compound was dissolved in 160 ml of ethanol and the solution was saturated with anhydrous gaseous hydrogenchloride at room temperature for 6 h. After 2 h of refluxing, the solution was evaporated to dryness *in vacuo*. The residue was added 50 ml of water and 15 ml of aqueous ammonium and the free base was extracted with chloroform. After drying with magnesium sulfate, the extract was evaporated *in vacuo*, which yielded 5.0 g of the oily base. Its neutralisation with oxalic acid dihydrate in 2-propanol yielded N,N-dimethyl-2-(2-(ethoxycarbonyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from 2-propanol melted at 151-154^{0}C.

Example 46:

N,N-Dimethyl-2-(3-(ethoxycarbonyl)phenylthio)benzylamine

A solution of 5.0 g of N,N-dimethyl-2-(3-carboxyphenylthio)benzylamine hydrochloride (Kmoníček V. et al.: Collect. Czech. Chem. Commun. 56, 2468 (1991)) in 200 ml of ethanol

was saturated with anhydrous gaseous hydrogenchloride for 8 h. The mixture was refluxed for 4 h and processed in analogy to example 45, which yielded 4.35 g (69%) of N,N-dimethyl-2-(3-(ethoxycarbonyl)phenylthio)benzylamine hydrogen oxalate, which after crystallisation from 2-propanol melted at 145-148^{0}C.

Example 47:

N,N-Dimethyl-2-(4-(ethoxycarbonyl)phenylthio)benzylamine.

A solution of 3.24 g of N,N-dimethyl-2-(4-carboxyphenylthio)benzylamine hydrochloride (see example 44) was saturated with anhydrous gaseous hydrogen chloride at 70-75^{0}C and under stirring for 3.5 h. The mixture was evaporated *in vacuo*, the oily residue was added 12 ml of 1.2M $NaHCO_3$ and the free base was extracted with ether. Drying and evaporating yielded 3.17 g of the oily base, which was neutralised with 1.26 g of oxalic acid dihydrate in 20 ml of ethanol at 60^{0}C. After cooling and adding of 2 ml of ether, 3.48 g (86%) of N,N-dimethyl-2-(4-(ethoxycarbonyl)phenylthio)benzylamine hydrogen oxalate crystallised, which after recrystallisation from 98% ethanol melted at 172-173.5^{0}C.

Example 48:

N,N-Dimethyl-2-(2-amino-4-(methoxycarbonyl)phenylthio)-benzylamine.

A suspension of 5.0 g of N,N-dimethyl-2-(2-(amino-4-(trifluoromethyl)phenylthio)benzylamine oxalate (see example 34) was made alkaline with aqueous ammonium and the free base was extracted with chloroform. The extract was dried with magnesium sulfate and evaporated. The residue base was heated with 8 ml sulfuric acid for 3 h up to 100^{0}C. After 16 h

of standing, 40 ml of methanol was added and the mixture was refluxed for 9 h. After pouring on the ice, it was made alkaline with aqueous ammonium and the free base was extracted with ether. From the extract 3.5 g of the oily base of N,N-dimethyl-2-(2-amino-4-(methoxycarbonyl)phenylthio)benzylamine was obtained. Its reaction with a solution of hydrogen chloride in ether provided the monohydrochloride, which after crystallisation from a mixture of ethanol and 2-propanol melted at 200-205^{0}C.

The following Table contains the values of serotonin re-uptake inhibition (5HT), noradrenaline re-uptake inhibition (NA) and paroxetine binding inhibition (PA) for some compounds prepared via the methods described in Examples hereinbefore in relation to the known compounds mentioned in the Background of the Invention hereinbefore.

T A B L E

Serotonin re-uptake inhibition (5HT) and noradrenaline re-uptake inhibition (NA) and paroxetine binding inhibition (PA).

Example No	IC_{50} (nmol/l)			Ratio IC_{50}
	5HT	NA	PA	NA/5HT
A-compound	4	4 890	18	1 222
B-compound	1.6	1 000	no data	625
14	0.01	272	13	27 200
16	0.01	128	7.5	12 800
24	0.01	588	32.5	58 800
26	0.01	2 730	4.3-6.5	273 000
34	0.02	9 100	0.7-5.7[a]	455 000
35	0.25	556	0.48	2 224

where

- IC_{50} is the concentration causing 50% inhibition of [^{3}H]paroxetine binding,
- a) means the IC_{50} values reached while repeated tests,
- compounds according to the invention are identified with example numbers and for testing are used in the form of their salts mentioned in Examples (Table values were calculated for the bases),
- and compounds A and B mean the known compounds;

A-compound = 1-(3-dimethylaminopropyl)-1-(4-fluorophenyl)-phthalato-5-carbonitrile)

and

B-compound=N,N-dimethyl-2-(4-(trifluoromethyl)-2-(hydroxy-methyl)phenylthio)benzylamine.

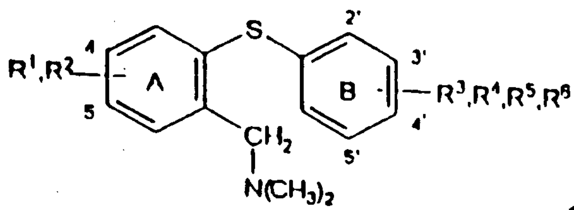
It is apparent that e.g. in case of the compound prepared via procedure according to example „34, that, in regard to the data concerning paroxetine binding inhibition in membrane fraction of rat brain, the corresponding compound according to the invention shows a good penetration through the blood-brain barrier.

Further, it is apparent that this compound does not show the affinity towards alpha-adrenergic muskarine and benzodiazepine receptors, so that it does not inhibit binding of [^{3}H] preparatives (prazosin, quinuclidinnyl benzilate and flunitrazepam) onto the receptors in the corresponding brain structures. This suggests a low probability of occurrence of some cardiovascular anticholinergic and central neurotropic effects of the benzodiazepine type compounds.

Derivatives of general formula (I) and their pharmaceutically acceptable salts are suitable for the production of pharmaceutical medicaments designed primarily for treatment and prophylaxis of depression, anxious states, migraine and other diseases of the central nervous system, in which the brain serotonin plays an important role.

C L A I M S

1. Derivatives of N,N-dimethyl-2-(arylthio)benzylamine of general formula (I)



(I)

or their salts with inorganic or organic acids which are pharmacodynamically harmless,

wherein at least one of the substituents R^1 and R^2 in the A ring in the 4 and 5 positions is a hydrogen atom, while the other substituent R^1 or R^2 in the A ring is either a fluorine or chlorine atom, and wherein two to three of the substituents R^3 to R^6 in the B ring in the 2 to 5 positions are hydrogen atoms,

while if the both substituents in the A ring are hydrogen atoms, the substituents in the B ring are

either three hydrogen atoms and one of the substituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group,

or are two hydrogen atoms, one fluorine or chlorine atom and one substituent formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylmethylthio, or nitro, or amino, or methoxy, or hydroxyl group,

or are two hydrogen atoms and each of the remaining two substituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group,

or are two hydrogen atoms and two fluorine or chlorine atoms;

or in case that one substituent in the A ring is either a fluorine or chlorine atom, the substituents in the B ring are

either two hydrogen atoms and two fluorine or chlorine atoms,

or two hydrogen atoms and one fluorine or chlorine atom and one of the subsituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino, or methoxy, or hydroxyl group,

or three hydrogen atoms and one fluorine or chlorine atom,

or one of the substituents formed by an alkyl with one to three carbon atoms, or trifluoromethyl, or methylsulfinyl, or hydroxymethyl - except the 2 position, or carboxyl - except the 3 position, or methoxycarbonyl, or ethoxycarbonyl, or methylthio, or nitro, or amino group.

2. N,N-Dimethyl-2-(2-amino-4-(trifluoromethyl)phenylthio)-benzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

3. N,N-Dimethyl-5-chloro-2-(4-methylthio)phenylthio)benzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

4. N,N-Dimethyl-5-fluoro-2-(4-methylthio)phenylthio)benzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

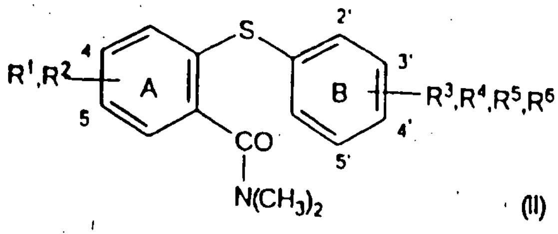
5. N,N-Dimethyl-2-(2,4-dichlorophenylthio)-5-fluorobenzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

6. N,N-Dimethyl-2-(3,4-dichlorophenylthio)-5-fluorobenzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

7. N,N-Dimethyl-2-(2-amino-4-(trifluoromethyl)-5-fluorophenylthio)benzylamine and its salts with pharmacodynamically harmless inorganic or organic acids.

8. Pharmaceutical medicament, designed primarily for treatment or prophylaxis of depressive states, characterized in that, that as an effective component contains a derivative of the compound of formula (I) according to claim 1, in the mixture with additives for pharmaceutical medicaments.

9. Methods of preparation of the derivatives of the compound of formula (I) according to claim 1, for which it is characteristic, that N,N-dimethylbenzamides of formula (II)

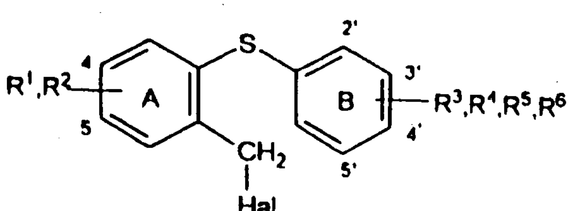


(II)

wherein the substituents R^1 to R^6 are identical to those in the formula (I), and besides that, in the B ring there can also be formyl or dimethylaminocarbonyl, are reduced by diborane generated *in situ* by the reaction of sodium borohydride with boron trifluoride etherate.

10. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, wherein one of the substituents R^3 to R^6 is an hydroxymethyl or dimethylaminomethyl group, by reduction of the compounds with formula (II) according to claim 9, wherein one of the substituents R^3 to R^6 in the B ring is an formyl, dimethylaminocarbonyl or carboxyl group, for which it is characteristic that an formyl, dimethylaminocarbonyl or carboxyl group is reduced at the same time.

11. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, for which it is characteristic that benzylhalogenides of formula (III)

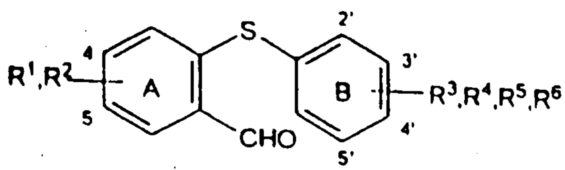


(III)

wherein the substituents R^1 to R^6 are identical to those in formula (I) and Hal is a chlorine or bromine atom, react with dimethylamine in an organic solvent at room temperature.

12. Method according to claim 11, characterized by that, that the reaction is carried out in toluene.

13. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, for which it is characteristic that benzaldehydes of formula (IV),



(IV)

wherein the substituents R^1 to R^6 are identical to those in formula (I), react with dimethylformamide and formic acid at 110 to 120 ^{0}C.

14. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, wherein one of the substituents R^3 to R^6 in the B ring is an methylsulfinyl group, for which it is characteristic that the corresponding methylthioderivative is oxidised by hydrogen peroxide in acetic acid at room temperature.

15. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, wherein one of the substituents R^3 to R^6 is ethoxycarbonyl, for which it is characteristic that the corresponding carboxyderivative is esterified by ethanol.

16. Method according to claim 15, for which it is characteristic that esterification is carried out in the presence of hydrogen chloride.

17. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, wherein one of the substituents R^3 to R^6 is an methoxycarbonyl group, for which it is characteristic that the corresponding trifluoro methyl-derivative is hydrolysed with sulfuric acid at 90 to 110 ^{0}C and subsequently esterified by methanol.

18. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, wherein one of the substituents R^3 to R^6 is an hydroxyl group, for which it is characteristic that the derivative of the compound of formula I, wherein one of the substituents R^3 to R^6 is an methoxyl group, demethylates.

19. Method according to claim 18, for which demethylation by heating with hydrobromic acid is characteristic.

20. Method of preparation of the derivatives of the compound of formula (I) according to claim 1, for which it is characteristic that the bases of derivatives of the compound of formula (I) are neutralised with pharmacodynamically harmless inorganic or organic acids.

21. Use of derivatives of the compound of formula (I) according to claim 1, in production of pharmaceutical medicaments designed particularly for treatment and prophylaxis of depressions, anxious states, migraine and other diseases of the central nervous system, in which brain serotonin plays an important role.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CZ 96/00022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C323/32 C07C323/37 C07C323/62 C07C323/63 A61K31/135
A61K31/235 A61K31/245 A61K31/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 56, no. 11A, November 1991, PRAGUE CS, pages 2468-2481, XP000647628 V. KMONICEK, ET AL.: "Potential antidepressants: 2-(fluoro-, chloro-, bromo- and cyanophenylthio)benzylamines as inhibitors of 5-hydroxytryptamine and noradrenaline re-uptake in brain" see the whole document ---	1,8,21

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
20 March 1997	01.04.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	English, R

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Inte   onal Application No
PCT/CZ 96/00022

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 56, no. 2, February 1991, PRAGUE CS, pages 459-477, XP000647627 K. SINDELAR, ET AL.: "Potential antidepressants and selective inhibitors of 5-hydroxytryptamine re-uptake in the brain: synthesis of several potential metabolites of moxifetin and of two A-ring fluorinated analogues" see the whole document ---	1,8,21
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 54, no. 12, December 1989, PRAGUE CS, pages 3294-3338, XP000647680 J. JILEK, ET AL.: "Potential antidepressants: 2-(methoxy- and hydroxyphenylthio)benzylamines as selective inhibitors of 5-hydroxytryptamine re-uptake in the brain" cited in the application see the whole document ---	1,8,21
A	COLLECTION OF CZECHOSLOVAK CHEMICAL COMMUNICATIONS, vol. 54, no. 7, July 1989, PRAGUE CS, pages 1995-2008, XP000647679 J. JILEK, ET AL.: "Potential antidepressants: 2-(Phenylthio)aralkylamines" cited in the application see the whole document ---	1,8,21
A	EP 0 396 827 A (SPOFA SPOJENE PODNIKY PRO ZDRAVOTNICKOU VYROBU) 14 November 1990 cited in the application see the whole document ---	1,8,21
A	WO 93 12080 A (WELLCOME FOUNDATION) 24 June 1993 cited in the application see the whole document ---	1,8,21
A	EP 0 402 097 A (WELLCOME FOUNDATION) 12 December 1990 see the whole document -----	1,8,21

2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/CZ 96/00022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 396827 A	14-11-90	NONE	
WO 9312080 A	24-06-93	AU 3091792 A	19-07-93
		ZA 9209590 A	10-06-94
EP 402097 A	12-12-90	AU 636892 B	13-05-93
		AU 5684190 A	13-12-90
		CA 2018307 A	06-12-90
		JP 3024052 A	01-02-91
		US 5095039 A	10-03-92
		US 5104897 A	14-04-92
		US 5216028 A	01-06-93

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(74) Agents: WURM, Bengt, R. et al.; AB Astra, Patent and Trade Mark Department, S-151 85 Södertälje (SE).

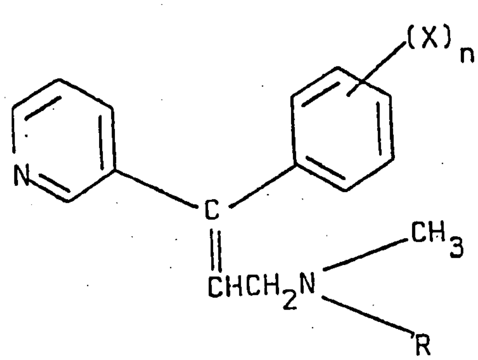
(81) Designated States: DK, FI, JP, NO, SU, US.

Published
With international search report

(54) Title: NOVEL HALOPHENYL-PYRIDYL-ALLYLAMINE DERIVATIVES

(57) Abstract

Compounds of the formula



wherein R is H or CH3, n is 1 or 2 and X is F, Cl, Br, I bound in an optional position to the phenyl group, provided that when X is Br it is bound in a position other than the 4 position, processes for their preparation and pharmaceutical preparations, methods of treatment employing such compounds. The compounds are useful for therapeutic treatment of various kinds of depressive conditions.

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Novel halophenyl-pyridyl-allylamine derivatives

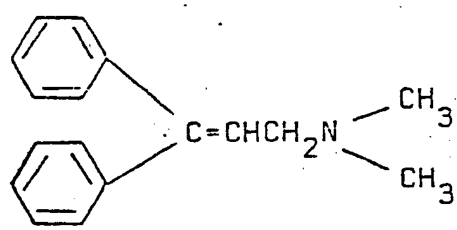
DESCRIPTION

Technical field

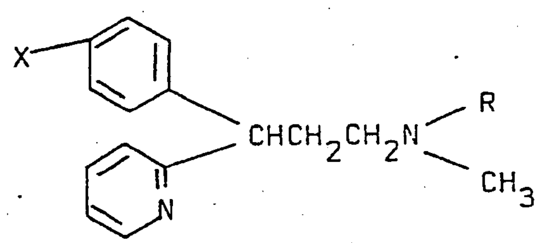
The present invention relates to new compounds having therapeutic activity and to methods for their preparation. The invention also relates to the preparation of pharmaceutical preparations containing at least one of the compounds and to methods for their pharmacological use.

Background art

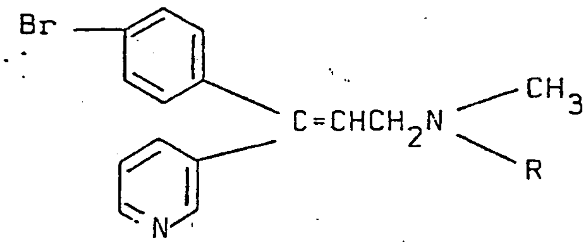
It is known from the literature that certain 1,1-diphenyl-3-aminoprop-1-enes, such as the compound having the formula



have an antidepressive effect, cf J. Med. Chem. 14, 161-4 (1971). Compounds having the formula



wherein X is chlorine or bromine and R is hydrogen or methyl, are described to have antidepressive effect, cf. US Patent No. 3,423,510. From the literature it is also known that compounds having the formula



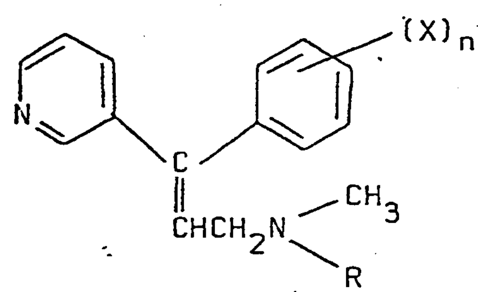
have antidepressive activity in animal models, cf. Belgian Patent Specifications No. 781,105 and No. 835,802.

Disclosure of invention

a) General outline

A main object of the present invention is to obtain new compounds having a good antidepressive effect. A further object of the invention is to obtain compounds having an antidepressive effect, and giving rise to only minor side-effects, in particular arrhythmogenic effects and anticholinergic effects. A further object is to provide antidepressive compounds useful for treatment of various kinds of depressions e.g. depressions connected with insufficient synaptic amounts of 5-hydroxytryptamine, noradrenaline or both. Further objects of the invention will be evident from the following description.

The compounds of the invention are characterized by the formula



I

wherein R is H or CH_3, n is 1 or 2, and X is a halogen selected from F, Cl, Br and I bound in an optional position to the phenyl group provided that when X is Br it is bound in a position other than the 4 position.

Pharmaceutically acceptable salts of these compounds are included within this invention.

Due to the lack of free rotation in the double bond the compounds of this invention may exist in different stereoisomeric forms, that is in cis-trans isomers or, according to the IUPAC nomenclature (J. Org. Chem. 35, 2849-2867, September 1970), in an E-form and a Z-form. The compound may be used therapeutically as a mixture of geometrical isomers or in pure E or Z form. The pure geometrical isomers may be prepared from an isomer mixture, from an isomer-pure starting material or directly by a stereoselective synthesis.

The compounds of this invention may be administered in the form of free bases or their salts with non-toxic acids. Some typical examples of these salts are the hydrobromide, hydrochloride, phosphate, sulphate, citrate, tartrate, malate and maleate.

b) Pharmaceutical preparations

In clinical practice the compounds of the present invention will be normally administered orally, rectally or by injection, in the form of pharmaceutical preparations comprising the active ingredient either as a free base or as a pharmaceutically acceptable, non-toxic acid addition salt, e.g. as the hydrochloride, hydrobromide, lactate, acetate, sulphate or sulphamate in association with a pharmaceutically acceptable carrier. Accordingly, terms relating to the novel compounds of this invention whether generical or specifical are intended to include both the free amine base and the acid addition salts of the free base, unless the context in which such terms are used, e.g. in the specific examples would be inconsistent with the broad concept. The carrier may be a solid, semisolid or liquid diluent, or a capsule. These pharmaceutical preparations constitute a further aspect of this invention.

Usually the active substance will constitute from 0.1 to 99 % by weight of the preparation, more specifically from 0.5 to 20 % by weight for preparations intended for injection and from 2 to 50 % by weight for preparations suitable for oral administration.

To produce pharmaceutical preparations containing a compound of the invention in the form of dosage units for oral application, the selected compound may be mixed with a solid pulverulent carrier, e.g. lactose, saccharose, sorbitol, mannitol, starches such as potato starch, corn starch or amylopectin, cellulose derivatives, or gelatine, and a lubricant such as magnesium stearate, calcium stearate or polyethylene glycol waxes, and then compressed to form tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, e.g. gum arabic, gelatine, talcum or titanium dioxide. Alternatively, the tablet can be coated with a lacquer dissolved in a readily volatile organic solvent or mixture of organic solvents. Dyestuffs may be added to these coatings in order to readily distinguish between tablets containing different active substances of different amounts of the active compound.

For the preparation of soft gelatine capsules (pearl-shaped closed capsules) consisting of gelatine and for example, glycerol or similar closed capsules, the active substance may be admixed with a vegetable oil, Hard gelatine capsules may contain granulates of the active substance in combination with solid, pulverulent carriers such as lactose, saccharose, sorbitol, mannitol, starches (e.g. potato starch, corn starch or amylopectin), cellulose derivatives or gelatine.

Dosage units for rectal application can be prepared in the form of suppositories comprising the active substance in admixture with a neutral fatty base, or gelatine rectal

capsules comprising the active substance in admixture with vegetable oil or paraffin oil.

Liquid preparations for oral application may be in the form of syrups or suspensions, for example solutions containing from about 0.2% to about 20% by weight of the active substance herein described, the balance being sugar and a mixture of ethanol, water, glycerol, and propyleneglycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethylcellulose as a thickening agent.

Solutions for parenteral applications by injection can be prepared in an aqueous solution of a water-soluble pharmaceutically acceptable salt of the active substance preferably in a concentration of from about 0.5% to about 10% by weight. These solutions may also contain stabilizing agents and/or buffering agents and may conveniently be provided in various dosage unit ampoules.

Suitable daily doses of the compounds of the invention at therapeutically treatment is 5 to 500 mg at peroral administration, preferably 50 to 250 mg and 1 to 100 mg at parenteral administration, preferably 10 to 50 mg.

c) Preferred embodiment

The preferred compounds of the invention are those compounds of formula I wherein R is H. A distinct embodiment of the invention is constituted by the compounds wherein n is 1. Compounds of formula I wherein X represents F or I are to be specifically mentioned. Among the compounds of formula I the geometrical isomers of compounds wherein X is 3-Cl or 4-Cl and R is CH_3 are to be mentioned as possessing an unexpected pharmacological profile.

Further, among the compounds of the invention the following are to be mentioned:

The group of compounds having a substituent X in the 2 position of the phenyl group comprising

3-(2-bromophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(2-bromophenyl)-N-methyl-3-(3-pyridyl)-allylamine,
3-(2,4-dichlorophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(2,4-dichlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine,
and
E-3-(2,4-dichlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine;

and the group of iodine or fluorine substituted compounds comprising

3-(4-iodophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(4-fluorophenyl)-N-methyl-3-(3-pyridyl)-allylamine,

and the group of pure Z isomeric compounds comprising

Z-3-(4-chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
and
Z-3-(4-chlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine;

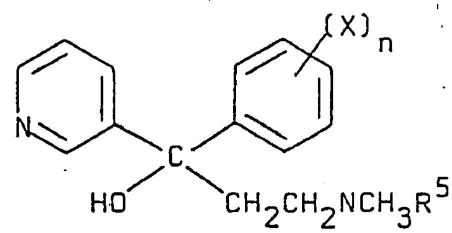
as well as the single members of said groups.

The pure or substantially pure geometrical isomers of the compounds of the invention constitute a further preferred embodiment. Especially preferred are the substantially pure isomers in which the pyridyl group and the mono- or di-methylamino groups are in cis configuration. In the IUPAC nomenclature such compounds are E forms when a substituent X

is in the 2 position and Z forms in other cases.

d) Methods of preparation

A. Dehydration of a compound of the formula



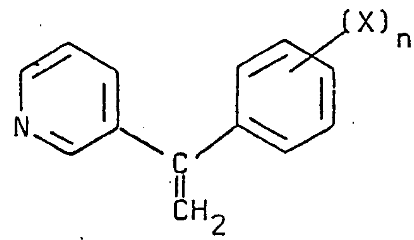
II

wherein n is 1 or 2, X is as defined above and R^5 is H, CH_3 or a removable protective group such as benzyl, trityl, 4,4'-dimethoxybenzhydryl, benzyloxycarbonyl, tert-butyloxycarbonyl, 9-anthrylmethyloxycarbonyl, or vinyloxycarbonyl, to a compound of the formula I, whereby a removable protective group R^5, when occurring, is split off by reduction or hydrolysis before, during or after the dehydration.

The dehydration of the starting material may for example be done by means of treatment with sulphuric acid and heating of the reaction mixture. The dehydration of the starting material may also be done by means of other types of acid-catalysis, such as by means of hydrochloric acid, phosphoric acid, potassium hydrogen sulphate, or oxalic acid. Other methods for the dehydration of the starting material to the formation of a compound of the formula I are dehydration using phosphoroxychloride in pyridine, and dehydration with thionylchloride in pyridine.

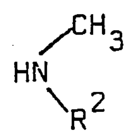
Also a catalytic dehydration of the starting material may be used. The dehydration is in this case carried out at a temperature of about 300 to 500°C using a catalyst such as kaolin, aluminium or aluminium oxide.

B. Treating a compound of the formula



III

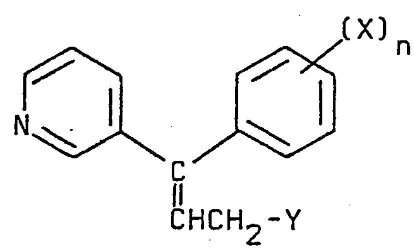
with formaldehyde and an amine of the formula



IV

whereby n and X are as defined above and R^2 is CH_3 or a removable protective group such as those mentioned under A above, to the formation of a compound of formula I.

C. Amination of a compound of the formula

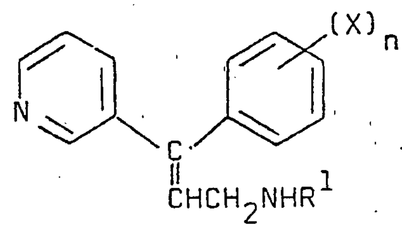


V

wherein n and X are as defined above and Y is a leaving group with an amine $HNCH_3R^5$ wherein R^5 is as defined above, to the formation of a compound of the formula I.

Illustrative examples of Y are halogens such as Cl, Br and I or sulphonates such as methanesulphonate, toluene-sulphonate and benzenesulphonate or ester functions such as a lower alkanoyloxy group, preferably having 2-4 carbon atoms, such as acetoxy.

D. Mono- or di-methylation of a primary amine or mono-methylation of a secondary amine all of the formula

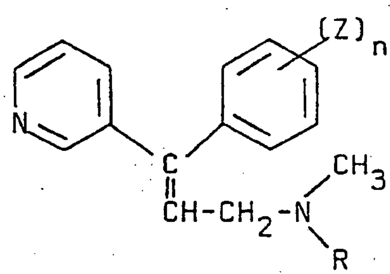


VI

wherein n and X are as defined above and R^1 is H or CH_3, to the formation of a compound of the formula I.

In the preparation of a secondary amine a protective acyl or sulphonyl group may first be introduced at the amino group. Such protective group is finally split off by hydrolysis.

E. Converting a compound of the formula

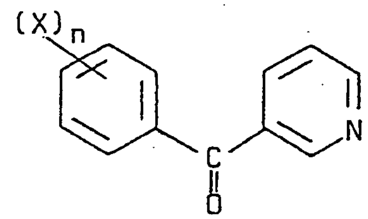


VII

wherein R is as defined above, n is 1 or 2, and Z is a replaceable moiety such as Cl, Br or I in an optional position, with position limitations as set out for X in formula I, into a compound of the formula I wherein X is Cl, Br or I in the same position as Z, however, X being different from Z. The conversion may be carried out by first converting the starting material to a metal-organic intermediate by reaction with e.g. butyl lithium and reacting the intermediate, e.g. a compound of the above

formula wherein Z is Li, with the desired halogen such as Cl_2, Br_2 or I_2 or a synthetic equivalent thereto, such as hexachloroethane, 2,3-dibromo-2,3-dimethylbutane or methylene iodide.

F. Conversion of a ketone of the formula



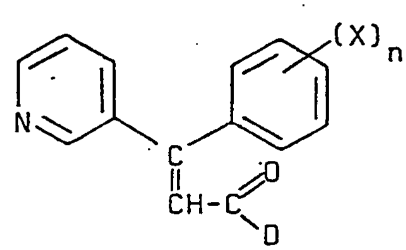
VIII

with a phosphorous ylide prepared either in situ or presynthesized by reaction of a compound of the formula

$$M{-}CH_2CH_2N\begin{matrix}\diagup CH_3\\ \diagdown R^2\end{matrix} \qquad IX$$

whereby X and R^2 are as defined above and M is $R^3_3P^+$, $R^4_3P^+$, $(R^4O)_2P(O)$, $R^3_2P(O)$, $(R^4_2N)_2P(O)$ or $(R^4O)_2P(S)$, and R^3 is a possibly substituted phenyl group and R^4 is an alkyl group having 1-5 carbon atoms, whereby an an-ion such as a halogen e.g. Br^- is present when M is $R^3_3P^+$ or $R^4_3P^+$, with a base such as butyl- or phenyllithium, sodium amide, sodium hydride or sodium alkoxide, to the formation of a compound of formula I.

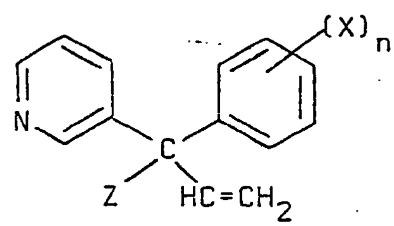
G. Reductive amination of an aldehyde or carboxylic acid of the formula



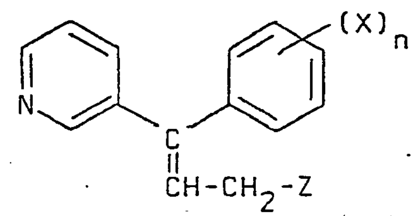
X

wherein D is H or OH, with methylamine or dimethylamine in the presence of a reducing agent, to the formation of a compound of formula I. The reducing agent can be e.g. sodium cyanoborohydride, sodium borohydride, formic acid, formamides or alcoholic potassium hydroxide. When D is OH sodium borohydride is preferably used with e.g. tetrahydrofuran as solvent. When D is H sodium cyanoborohydride may be used in an alcoholic solution.

H. Palladium catalyzed amination of compounds of the following formulas

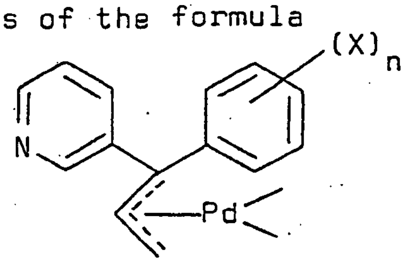


or



XI XII

wherein Z is a leaving group such as hydroxy, alkoxy, alkanoyloxy such as acetoxy, or chloro, with dimethylamine or methylamine. Generation of the intermediate π-allylpalladium complexes of the formula

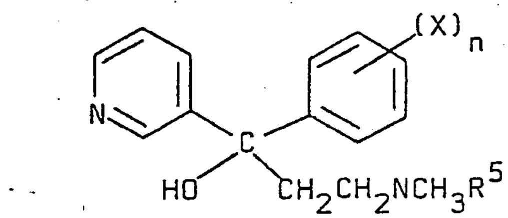


may be accomplished with a catalyst such as $Pd(Ph_3P)_4$, Pd black, $Pd(AcAc)_2$ or $Pd(OAc)_2$ preferably in the presence of a ligand such as Ph_3P or 1,2-bis(diphenylphosphino)ethane.

e) <u>Intermediates</u>

For the preparation of the compounds of formula I it has been found that certain hitherto unknown compounds may be valuable.

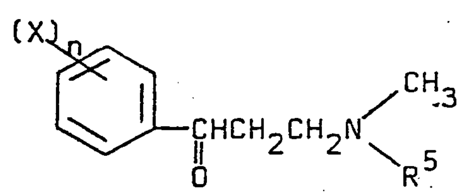
When preparing the compounds of formula I according to process A compounds of the formula



II

wherein R, n and X are as defined above are used as starting materials.

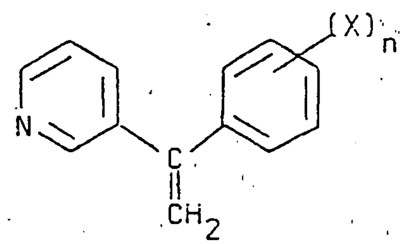
These starting materials may be prepared by reacting a compound of the formula



XIII

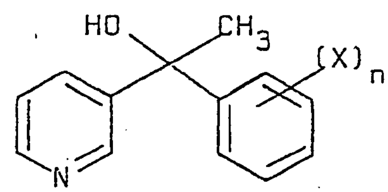
in which formula n, X and R^5 have the meanings indicated above, with 3-pyridyllithium, whereafter when R denoting H is desired, a protective group R^5 is split off. Alternatively such protective group may be split off after or during dehydration to a corresponding allylamine, whereby the splitting gives a secondary amine of formula I.

When preparing compounds of the formula I according to process B compounds of the formula



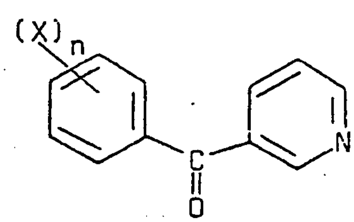
III

wherein n and X are as defined above, are used as starting material. This starting material can be prepared by dehydration of



XIV

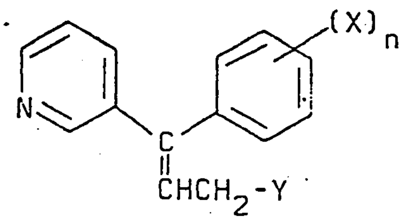
or by a Wittig reaction of the ketone



VIII

The intermediates constitute a further aspect of the invention.

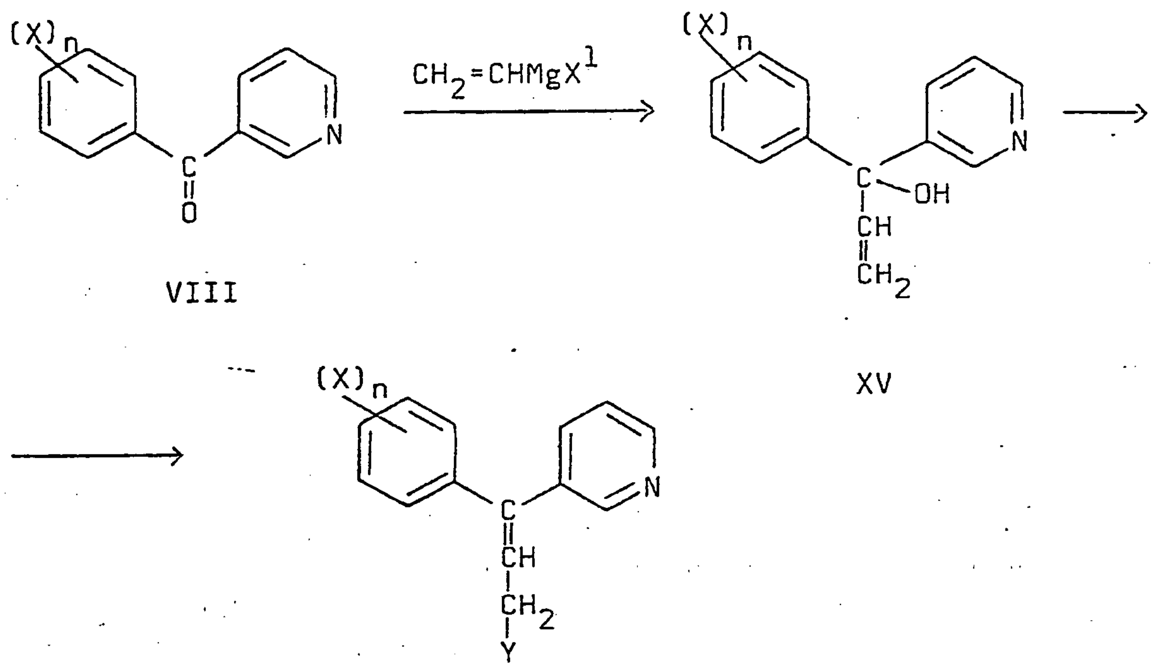
When preparing the compounds of the formula I according to process C compounds of the formula



V

wherein Y is a leaving group are used as starting material.

This starting material can be prepared according to the reaction scheme



VIII

XV

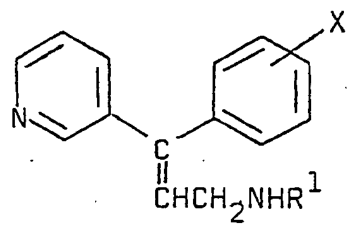
V

wherein n, X and Y are as defined above and X^1 is Cl, Br or I.

The allylic tertiary alcohol of formula XV is a further useful novel intermediate. In addition to its utility for preparation of the starting material for process C it is also useful in other reaction routes finally producing the compound of formula I, such as process G, as will be further described below. Further, an alkancarboxylic ester of the tertiary alcohol XV is a useful intermediate, as further described in other parts of this specification.

The tertiary alcohol XV is thus obtainable by a Grignard synthesis from the corresponding ketone. An allylic rearrangement introducing the group Y may be produced by employing one of the following reagents; aqueous hydrochloric acid, aqueous hydrobromic acid, phosphorus trichloride, thionylchloride, phosphorus pentachloride or another halogenating agent or methylsulfonic or toluenesulfonic acid.

When preparing the compound of the formula I according to process D a compound of the formula



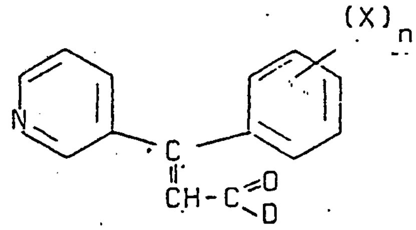
VI

is used as starting material. The preparation of this compound is described in paragraph d), when R^1 is CH_3. When R^1 is H processes in analogy with processes A or C may be employed.

Starting materials for process E are obtainable by processes known in the art, or described in paragraph d) above.

Starting materials for process F are obtainable by processes known in the art.

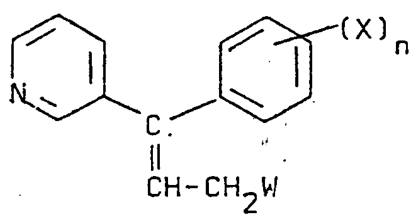
When preparing the compound of formula I according to process G a compound of the formula



X

in which formula D is H or OH and n and X are as defined above, is used as starting material.

The aldehyde (D is H) starting material may be prepared by oxidation of a compound of formula

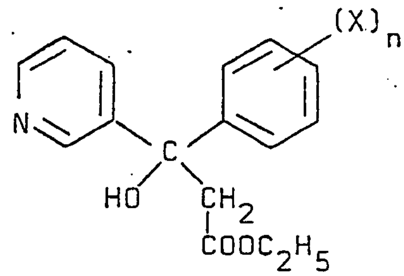


XVI

wherein W is OH or a leaving group Y, NR'R", NR'H, NH_2 or $\underset{\downarrow}{NR'R"}$ O, wherein R' and R" are alkyl groups having 1-4 carbon atoms, with reagents such as manganese dioxide, dimethyl sulfoxide, silver(I), silver(II), iron(III), chromium trioxide reagents, aluminium alkoxides, nickel peroxide, lead tetraacetate and 2,3-dichloro-5,6-dicyanobenzoquinone or by oxidation in one step from a compound of the formula XV above with an appropriate reagent mentioned above, such as chromic acid/sulfuric acid.

The carboxylic acid (D is OH) starting material may be prepared by further oxidation of the aldehyde mentioned above or by direct oxidation of a compound of formula

XVI above wherein W preferably represents a hydroxy group with reagents like nickel peroxide, silver oxide, selenium dioxide, manganese dioxide, chromic acid, permanganate or Pt/O_2. Alternatively, the acrylic acids (XI, D=OH) may be prepared by dehydration and hydrolysis of



XVII

which are obtainable by a Reformatsky reaction from 3-pyridyl aryl ketones.

The intermediate alcohol of formula XVI may be prepared by acid catalyzed rearrangement of the corresponding tertiary allylic alcohol of formula XV with acids such as sulfuric acid, phosphoric acid or p-toluenesulfonic acid, and if required subsequent introduction of a leaving group or amino function as described above.

The starting materials of formulas XI and XII employed in process H are obtainable in the manner described for compounds XV and V above with introduction of the group Z when required.

The allylic tertiary alcohols used in the different processes described above are consolidated in formula XI above. In said formula the group Z may contain 1-4 carbon atoms.

f) Working examples

Preparation of Intermediates

Example A

2-(3-Chlorobenzoyl)-N,N-dimethylethylamine hydrochloride

3-Chloroacetophenone (35.8 g, 0.23 mol), dimethylamine hydrochloride (28.1 g, 0.345 mol), paraformaldehyde (13.8 g, 0.46 mol) and concentrated hydrochloric acid (0.75 ml) were refluxed in 60 ml ethanol for 5 h.

After cooling the precipitated hydrochloride was collected and dried in vacuo. Yield 42.3 g (86 %). M.p. 189-191°C. Recrystallisation from ethanol / water (15:1) gave the pure product. M.p. 193-195°C.

3-(3-Chlorophenyl)-N,N-dimethyl-3-hydroxy-3-(3-pyridyl) propylamine

To a solution of butyllithium (61 ml of a 1.5 M solution in hexane, 92 mmol) in 25 ml ether at -50° to -60°C 3-brompyridine (15.2 g, 96 mmol) was added in 40 min. After stirring for 15 min 2-(3-chlorophenyl)-N,N-dimethylethylamine (16.9 g, 80 mmol) in 25 ml ether was added at about -50°C in 1 h. After stirring at -40° to -50°C for 2 h the mixture was poured on 120 ml water and 14 ml concentrated hydrochloric acid. The pH was adjusted to about 6 and the solution extracted with petroleum

ether (80-110°C).

The aqueous phase was made alkaline (pH 10.5) and extracted with ether. The ether phase was dried and evaporated to yield 21.4 g brown oil which crystallized. The solid was triturated with petroleum ether (80-110°C) and then recrystallized from petroleum ether (80-110°C) to give 9.6 g (41%) white crystals. M.p. 102-104°C. Preparation of an end compound from the intermediate obtained is described in Example 1.

Example B

1-(4-Chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol

A solution of vinylbromide (11.8 g, 110 mmol) in 40 ml tetrahydrofuran was added to a mixture of magnesium (2.79 g, 115 mmol) in 20 ml tetrahydrofuran under a nitrogen atmosphere at 50 to 60°C. After reflux for 1 h 3-(4-chlorobenzoyl)pyridine (21.8 g, 0.100 mol) in 100 ml tetrahydrofuran was added at 10°C. After stirring for 1 h a solution of 8 g ammonium chloride in 40 ml water was added and the mixture filtrated. The organic phase was dried over sodium sulphate and evaporated to give 29.4 g of a red oil containing 20% unreacted starting ketone. This crude product was used directly in the next step (Example C).

Example C

3-Chloro-1-(4-chlorophenyl)-1-(3-pyridyl)-1-propene

A solution of crude 1-(4-chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol (40 mmol) in 100 ml methylene chloride was added dropwise to a suspension of phosphorus pentachloride (12.4 g, 60 mmol) at 10°C. After stirring for 1 h at room temperature the solution was washed with 50 ml water at 0 to 10°C. The solution of the crude title compound was used

in the following aminations, i.e. Example 2 and 3.

Example D

1-(4-Chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol

A solution of vinylbromide (38.4 g, 359 mmol) in 100 ml tetrahydrofuran was added to a mixture of magnesium (9.15 g, 377 mmol) in 40 ml tetrahydrofuran under a nitrogen atmosphere at 50 to 60°C. After reflux for 1 h 3-(4-chlorobenzoyl)pyridine (62.4 g, 287 mmol) in 250 ml tetrahydrofuran was added at 10°C. After stirring for 1 h a solution of 20 g ammonium chloride in 100 ml water was added and the mixture filtered. The organic phase was evaporated and the residue taken up in ether and treated with charcoal. After filtration the solvent was evaporated to give 62.6 g (89%) of a brownish oil which solidified. Recrystallisation from toluene gave a product having m.p. 82.5-84°C.

The allylic alcohols according to Examples E-H were prepared in analogy with the above procedure in Example D. Preparation of end compounds from the intermediates is described in Examples 4-10.

Example E

1-(4-Fluorophenyl)-1-(3-pyridyl)-2-propen-1-ol. 85% yield. Oil.

Example F

1-(2-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol. 86% yield. M.p. 111-112°C.

Example G

1-(3-Bromophenyl)-1-(3-pyridyl)-2-propen-1-ol. 90% yield. Oil.

Example H

1-(2,4-Dichlorophenyl)-1-(3-pyridyl)-2-propen-1-ol. 88% yield. M.p. 111-112^{o}C.

Example I

(Z)-3-(4-Chlorophenyl)-3-(3-pyridyl)-2-propenal

A mixture of 2.5 mmol 3-(4-chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine and 7 g manganese dioxide in 25 ml chloroform was stirred at reflux for 1.5 h under nitrogen. An additional portion of 5 g manganese dioxide was added and after stirring for another 2 h. The mixture was filtered and the solvent evaporated to leave 0.58 g (84%) of a yellow oil.
TLC revealed no starting amine. ^{1}H NMR ($CDCl_3$) showed the typical signals at δ 6.7 (d, J=8 Hz, vinyl), 8.7 (m, 2-pyridyl), 8.85 (dd, 6-pyridyl) and 9.6 (d, J=8 Hz, aldehyde) ppm. The crude product was used directly in the reductive methylamination according to Example 14 below.

Example J

3-(4-Chlorophenyl)-3-(3-pyridyl)-2-propen-1-ol

1-(4-Chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol (0.33 g) was stirred in 25 ml 2 M sulfuric acid overnight at 50^{o}C. The reaction mixture was made alkaline with 45% sodium hydroxide and extracted with ether. The ethereal layer was dried ($MgSO_4$) and evaporated to give 0.30 g of the title

compound as an oil. ^1H NMR ($CDCl_3$) revealed an approximate Z/E ratio of 60/40: δ 3.8 (Br, OH), 4.20 and 4.25 (two doublets, allyl), 6.37 and 6.30 (two triplets, vinyl), 6.9-7.6 (aromatic) and 8.3-8.6 (multiplet, 2,6-pyridyl). This crude product was used directly in the oxidation step according to Example K.

Example K

3-(4-Chlorophenyl)-3-(3-pyridyl)-2-propenal

A mixture of 0.30 g 3-(4-chlorophenyl)-3-(3-pyridyl)-2-propen-1-ol and 1.5 g manganese dioxide in 15 ml chloroform was stirred overnight at room temperature under nitrogen. Filtration and evaporation of the solvent gave 0.30 g of a yellow oil, which contained the isomeric aldehydes in a Z/E ratio of circa 60/40 according to NMR. The crude product was used directly in the reductive dimethylamination according to Example 15.

Example L

3-Acetoxy-3-(4-chlorophenyl)-3-(3-pyridyl)-1-propene

A mixture of 1-(4-chlorophenyl)-1-(3-pyridyl)-2-propen-1-ol (0.692 g, 2.8 mmol), triethylamine (3.3 ml) and 4-dimethylaminopyridine (85 mg) was stirred in acetic anhydride (0.9 ml) at 25°C for 20 h. Methanol (1 ml) was added and after 10 min the mixture was concentrated in vacuo. Ether (25 ml) was added and the ether phase was washed with saturated $NaHCO_3$ solution (3×15 ml) and dried over $MgSO_4$. Evaporation of the solvent gave 0.725 g (90%) of the title compound, which was used in the palladium catalyzed amination according to Example 16.

Preparation of End Compounds

In the examples below NMR and mass spectra are in accordance with the structures indicated.

Example 1

(Z)-3-(3-chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate (Method A)

A solution of 3-(3-chlorophenyl)-N,N-dimethyl-3-hydroxy-3-(3-pyridyl)-propylamine (4.45 g, 15 mmol) in 5 ml glacial acetic acid and 3.3 ml concentrated sulphuric acid was refluxed for 1 h. After cooling 25 ml water was added and pH adjusted with concentrated ammonia solution to 9.5. The mixture was extracted with ether. The ether phase was dried and evaporated to yield 3.6 g (88%) of a brown oil. The crude product was found to hold the diastereomers in a Z/E isomeric ratio of 72/28 according to GLC. The base mixture was dissolved in 20 ml acetone and one equivalent of oxalic acid in acetone was added to precipitate the title compound. This was recrystallized from ethanol to give a white crystalline substance with less than 0.5% of E-isomer according to GLC and NMR. M.p. 171-174^{o}C.

Example 2

(Z)-3-(4-chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate (Method C)

A solution of crude 3-chloro-1-(4-chlorophenyl)-1-(3-pyridyl)-1-propene (40 mmol) was added to dimethylamine (18.0 g, 400 mmol) in 25 ml methylene chloride at 10^{o}C. After stirring at room temperature for 1.5 h 25 ml water were added, the phases separated and the solvent removed from the organic phase. The residue was taken up in ether and

extracted with dilute hydrochloric acid to pH 4.5. The aqueous phase was made alkaline, extracted with ether and the solvent removed. The residual oil (6.8 g) was dissolved in acetone and one equivalent of oxalic acid in acetone was added. The precipitated oxalate was recrystallized twice from ethanol to give 5.1 g (35%) of pure product mainly (95%) containing the Z-isomer. M.p. 164-168°C. UV (0.1 M HCl): λ_{max} 246 nm and λ_{min} 224 nm <u>cf</u> 4-bromo analogue: λ_{max} 250 nm and λ_{min} 225 nm. Acta Pharm. Suecica <u>16</u>, 299 (1979). ^{1}H-NMR ($CDCl_3$, base): δ 2.23 (s, CH_3), 3.01 (d, allyl), 6.30 (t, vinyl), 7.0-7.6 (aromatic), 8.45 (m, 2-pyridyl) and 8.6 (dd, 6-pyridyl).

Example 3

3-(4-Chlorophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate (Method C)

Z-isomer

The title compound was prepared in analogy with the tertiary amine according to Example 2 from the crude 3-chloro-1-(4-chlorophenyl)-1-(3-pyridyl)-1-propene and methylamine with the following exceptions. Ethanol was used as cosolvent during the amination and the crude oxalate was recrystallized from ethanol/water (3:1). The yield of pure product was 23% of mainly (97%) the Z-isomer according to HPLC and UV. M.p. 203-204.5°C. UV (0.1 M HCl): λ_{max} 245 nm and λ_{min} 224 nm. (<u>cf</u> 4-bromoanalogue: λ_{max} 248 nm and λ_{min} 224 nm. Acta Pharm. Suecica <u>16</u>, 299 (1979).

E-isomer

From the mother liqour of the above recrystallization a sample was purified by HPLC (reversed phase system Nucleosil 5μ, methanol-phosphate buffer pH 3.0 40+60). The methanol was evaporated and the aqueous solution was made alkaline and extracted twice with ether. After drying ($MgSO_4$) the ethereal solution was concentrated in vacuo leaving an oil having a UV spectra in accordance with the E-configuration.
UV (0.1 M HCl): λ_{max} 219 nm and 235 nm (shoulder)
cf 4-bromoanalogue λ_{max} 220 nm and 236 nm (shoulder)
Acta Pharm. Suecica 16, 299 (1979).

The compounds obtained by Examples 4-10 were prepared by Method C according to Examples 2 and 3 from the corresponding allylic alcohols after allylic rearrangement to the corresponding allylic chlorides according to Example C.

Example 4

3-(4-Fluorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate. 40% yield. M.p. 151-155°C.

Example 5

3-(4-Fluorophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate. 30% yield. M.p. 196-198°C.

Example 6

(E)-3-(2-Bromophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate. M.p. 148-149°C.

Example 7

(E)-3-(2-Bromophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate. M.p. 200-202°C.

Example 8

(Z)-3-(3-Bromophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate. 21% yield. M.p. 198-199°C.

Example 9

(E)-3-(2,4-Dichlorophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine oxalate. 25% yield. M.p. 167-169°C.

Example 10

(E)-3-(2,4-Dichlorophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate. M.p. 203-205°C.

Example 11

(Z)-3-(4-iodophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate (Method E)

Butyllithium (10 mmol) in 10 ml hexane was injected through a septum to a stirred solution of (Z)-3-(4-bromophenyl)--N,N-dimethyl-3-(3-pyridyl)allylamine (3.2 g, 10 mmol) in 30 ml dry tetrahydrofuran under a nitrogen atmosphere at -65°C. The deep red solution was stirred for 0.5 h at -65°C and then iodine (2.54 g, 10 mmol) was added. The mixture was stirred for an additional 0.5 h at -65°C and then allowed to reach room temperature during 1.5 h. Water was added, the tetrahydrofuran evaporated and the residue extracted with ether. The ether phase was washed with sodium bisulphite, dried over magnesium sulphate and evaporated to give 2.7 g of an oil. This residue was dissolved in

hydrochloric acid at pH 5.9 and extracted with 1,2-dichloroethane. The organic phase was evaporated to give a residue of 1.8 g which was triturated three times with ether, leaving 1.0 g of the off-white crystalline hydrochloride. This product was converted to the base (0.7 g, 20%) and crystallized as the oxalate from ethanol/isopropyl ether. M.p. 170-173°C.

Example 12

3-(3-Bromophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine oxalate (Method F)

Butyllithium in hexane (10.5 mmol) was injected to a mixture of 4.34 g (10.5 mmol) dimethylaminoethyl triphenylphosphoniumbromide and 25 ml dry tetrahydrofuran at ambient temperature. After stirring for 15 min a solution of 2.62 g (10 mmol) 3-(3-bromobenzoyl)pyridine in 20 ml dry tetrahydrofuran was injected to the solution of the dark red ylide. The mixture was heated to 60°C and stirred overnight. After cooling and addition of 75 ml 2 M hydrochloric acid the solution was extracted with 100 ml toluene. The organic layer was extracted with 50 ml 2 M hydrochloric acid. The combined aqueous phases were washed with 3×50 ml toluene, made alkaline and extracted twice with ether. Drying ($MgSO_4$) and evaporation of the ethereal phase gave 2.9 g (91%) of the base as a yellow oil.
^1H NMR of the base in $CDCl_3$ showed the characteristic overlapping signals of the mixture of the diastereomers (Z and E forms), i.e. δ 2.2 ppm (singlet, methyl), 3.0 ppm (doublet, allyl), 6.3 ppm (triplet, vinyl) and 8.6 ppm (multiplet, 2,6-pyridyl). Integration of a $Eu(fod)_3$ [tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionato)europium] shifted ^1H NMR showed the Z/E isomeric ratio to be 53/47. GLC revealed no other compounds and the Z/E ratio was determined to 56/44.

Z-isomer

The base mixture (2.7 g, 8.5 mmol) was dissolved in hot acetone and 0.9 ml (10 mmol) conc. hydrochloric acid was added. The mixture was cooled and the acetone was decanted from the semisolid precipitate, which consists of 1.7 mmol pure Z-form according to GLC and NMR. The product was converted to base and then oxalate, which was recrystallized from ethanol/isopropyl ether to give 0.53 g (1.3 mmol) of the title compound. M.p. 162-163^{o}C.

Example 13

(Z)-3-(4-Chlorophenyl)-N-methyl-3-(3-pyridyl)allylamine oxalate (Method G)

To 2.1 mmol crude (Z)-3-(4-chlorophenyl)-3-(3-pyridyl)-2-propenal, in a flask, was added in the following order: 0.68 g (10 mmol) methylamine hydrochloride, 10 ml methanol, 0.36 g (9 mmol) sodium hydroxide, 0.13 g (2 mmol) sodium cyanoborohydride and 5 g molecular sieves (3Å). The mixture was stirred under nitrogen for 3 days and then 75 ml 2 M hydrochloric acid was added. After filtration the aqueous solution was made alkaline, extracted twice with ether and dried over $MgSO_4$. Evaporation gave 0.2 g (0.77 mmol) of an oil, which was dissolved in hot ethanol. Oxalic acid (0.7 mmol, 0.09 g) was added and the title compound precipitated from the solution to give 0.15 g (20%) of a white crystalline substance. M.p. 203.5-204^{o}C. The MS was identical with the MS for the same compound prepared according to Example 3, and HPLC showed a Z/E ratio of 95/5.

Example 14

3-(4-Chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine

To 0.25 g (1 mmol) crude 3-(4-chlorophenyl)-3-(3-pyridyl)-2-propenal, in a flask, was added in the following order: 0.73 g (9 mmol) dimethylamine hydrochloride, 10 ml methanol, 0.24 g (6 mmol) sodium hydroxide, 0.094 g (1.5 mmol) sodium cyanoborohydride and 5 g molecular sieves (3 Å). The mixture was stirred at room temperature under nitrogen for 3 days and then 100 ml methanol were added. After filtration the methanol was evaporated and the residue dissolved in a hydrochloric solution at pH 4.9 and washed with ether twice. The aqueous solution was made alkaline, extracted twice with ether and dried over $MgSO_4$. Evaporation gave 0.18 g (66%) of pure title compound as an isomeric mixture having an approximate Z/E ratio of 54/46 (NMR).

(E)-3-(4-Chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine

A sample of the above Z/E mixture was eluted three times on preparative TLC plates (0.2 mm, 20×20 cm) with ethyl acetate/methanol/triethylamine (21/4/1). The lower band containing the E-isomer was collected and washed with methanol/dichloromethane. The solvent was evaporated to leave an oil having UV and ^1H NMR in accordance with the E-configuration.

UV (0.1 M HCl): λ_{max} 218 nm and 235 nm (shoulder). (cf 4-bromo analogue: λ_{max} 219 nm and 237 nm (shoulder). Acta Pharm. Suecica 16, 299 (1979)).
^1H NMR ($CDCl_3$): δ 2.22 (s, CH_3), 3.04 (d, allyl), 6.27 (t, vinyl), 7.0-7.6 (aromatic), 6.55 (dd, 6-pyridyl) and 8.6 (m, 2-pyridyl).

Example 15

3-(4-Chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)allylamine (Method H)

Palladium acetylacetonate (9.3 mg, 0.03 mmol), 1,2-bis-(diphenylphosphino)ethane (17.5 mg, 0.04 mmol) and 3-acetoxy-3-(4-chlorophenyl)-3-(3-pyridyl)-1-propene (0.211 g, 0.73 mmol) was dissolved in tetrahydrofuran (2.2 ml) at room temperature under nitrogen. A solution of dimethylamine in tetrahydrofuran (3.2 ml of a 2.5 M solution) was added. The resulting solution was warmed to 55^{o}C and allowed to react for 1 h and 40 min. Evaporation of the solvent and work-up by preparative TLC (SiO_2, ethyl acetate/hexane/triethylamine 49/49/2) gave 0.158 g (79%) of a Z/E mixture of the title compound. The Z/E ratio was determined by ^{1}H NMR to 55/45.

Example 16. Preparation of soft gelatin capsules

500 g of active substance were mixed with 500 g of corn oil, whereupon the mixture was filled in soft gelatin capsules, each capsule containing 100 mg of the mixture (i.e. 50 mg of active substance).

Example 17. Preparation of soft gelatin capsules

500 g of active substance were mixed with 750 g of pea nut oil, whereupon the mixture was filled on soft gelatine capsules, each capsule containing 125 mg of the mixture (i.e. 50 mg of active substance).

Example 18. Preparation of tablets

50 kg of active substance were mixed with 20 kg of silicic acid of the trade mark Aerosil. 45 kg of potato starch and

50 kg of lactose were mixed therewith and the mixture was moistened with a starch paste prepared from 5 kg of potato starch and distilled water, whereupon the mixture was granulated through a sieve. The granulate was dried and sieved, whereupon 2 kg of magnesium stearate was mixed into it. Finally the mixture was pressed into tablets each weighing 172 mg.

Example 19. Preparation of an emulsion

100 g of active substance were dissolved in 2500 g of pea nut oil. From the solution thus obtained, 90 g of gum arabic, aroma and colouring agents (q.s.) and 2500 g of water an emulsion was prepared.

Example 20. Preparation of a syrup

100 g of active substance were dissolved in 300 g of 95% ethanol, whereupon 300 g of glycerol, aroma and colouring agents (q.s.) and 1000 ml of water were mixed therein. A syrup was obtained.

Example 21. Preparation of an injection solution

Active substance (hydrobromide) (1 g), sodium chloride (0.8 g) and ascorbic acid (0.1 g) are dissolved in sufficient amount of distilled water to give 100 ml of solution. This solution, which contains 10 mg of active substance per ml, is used in filling ampoules, which are sterilized by heating at 120°C for 20 minutes.

Example 22. Preparation of effervescing tablets

100 g of active substance, 140 g of finely divided citric acid, 100 g of finely divided sodium hydrogen carbonate, 3.5 g of magnesium stearate and flavouring agents (q.s.) were mixed and the mixture was pressed into tablets each containing 100 mg of active substance.

Example 23. Preparation of a drop solution

100 g of active substance were mixed with 300 g of ethanol, whereupon 300 g of glycerol, water to 1000 ml, aroma and flavouring agents (q.s.) and 0.1 N sodium hydroxide solution (to pH 4.5 to 5.5) was added while stirring. A drop solution was obtained.

Example 24. Preparation of a sustained release tablet

200 g of active substance were melted together with 50 g of stearic acid and 50 g of carnauba wax. The mixture thus obtained was cooled and ground to a particle size of at most 1 mm in diameter. The mixture thus obtained was mixed with 5 g of magnesium stearate and pressed into tablets each weighing 305 mg. Each tablet thus contains 200 mg of active substance.

g) Pharmacological tests

It is not possible by experimental means to induce depressions in laboratory animals. In order to evaluate a possible anti-depressive effect of new substances bio-chemical-pharmacological test methods must be resorted to. One such method, which seems to give a good indication of the potential anti-depressive effects of the test substance, is described in Europ. J. Pharmacol. 17, 107, 1972.

This method involves the measurement of the decrease in the uptake of ^{14}C-5-hydroxytryptamine (^{14}C-5-HT) and ^{3}H-nor-adrenaline (^{3}H-NA) in brain slices from mice after in vivo and in vitro administration of the test substance.

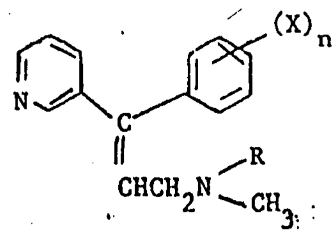
Inhibition of the uptake of ^{14}C-5-HT and ^{3}H-NA in vitro and in vivo

The test substances were administered intraperitoneally half an hour before the animals were killed. The hypothalamus was taken out, sliced and incubated in a mixture consisting of 1×10^{-7} M of ^{14}C-5-HT, 1×10^{-7} M of ^{3}H-NA, 5.6 mM glucose, 5×10^{-5} M pargyline, 1.1 mM ascorbic acid and 1.3×10^{-4} $EDTANa_2$ in 2 ml of Krebs-Henseleit buffer, pH 7.4 per 20 mg of brain slices. The incubation time was 5 minutes with 5 minutes of pre-incubation before the labelled amines were added. The slices were dissolved in Soluene® and the amounts of radioactive amines taken up were determined by liquid scintillation. The doses producing 50 per cent decrease of the active uptake (ED_{50}) of ^{14}C-5-HT and ^{3}H-NA were determined by linear regression analysis of log dose response curves. Active uptake is defined as that part of the radioactive uptake which is inhibited by a high concentration of cocaine.

In the in vitro method slices of mouse midbrain were pre-incubated for 5 minutes with solution of the compound to be tested and then incubated as described above.

TABLE

Inhibition of neuronal uptake of 5-hydroxytryptamine and noradrenaline in slices from mouse brain

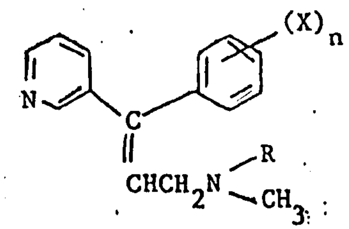


Example No.	X	R	isomer	salt or base	Uptake of ^{14}C-5-HT in vitro EC_{50} µM	Uptake of ^{14}C-5-HT in vivo ED_{50} µmole/kg i.p.	Uptake of ^{3}H-NA in vitro EC_{50} µM	Uptake of ^{3}H-NA in vivo ED_{50} µmole/kg i.p.
Prior art compounds	Imipramine			hydrochloride	0.3	125	0.08	63
	4-Br	H	Z	hydrochloride	0.1	15	1.5	>101 (38%) x
	4-Br	H	E	oxalate	2.5	102	0.8	25
	4-Br	CH_3	Z	hydrochloride	1.7	49	24.4	>98 (26%) x
	4-Br	CH_3	E	oxalate	6.1	>98 (36%) x	6.1	25
3	4-Cl	H	Z	oxalate	0.4	19	1.1	23
2	4-Cl	CH_3	Z	oxalate	1.1	34	1.1	46
5	4-F	H		oxalate	2.4	72	9	29
4	4-F	CH_3		oxalate	4	115	29	72
11	4-I	CH_3	Z	oxalate	1.3	46	> 22 (33%) x	>88 (0%) x
1	3-Cl	CH_3	Z	oxalate	2.7	>110 (12%) x	10	>110 (41%) x

x Percentage inhibition at the highest dose (concentration) examined is given in brackets.

TABLE (continued)

Inhibition of neuronal uptake of 5-hydroxytryptamine and nor-adrenaline in slices from mouse brain



Example No.	X	R	isomer	salt or base	Uptake of ^{14}C-5-HT in vitro EC_{50} µM	Uptake of ^{14}C-5-HT in vivo ED_{50} µmole/kg i.p.	Uptake of ^{3}H-NA in vitro EC_{50} µM	Uptake of ^{3}H-NA in vivo ED_{50} µmole/kg i.p.
8	3-Br	H	Z	oxalate	1.4	>102	0.9	58
12	3-Br	CH_3	Z	oxalate	0.9	> 98	4.2	66
	2-Br	H	E/Z 1:1	base	1.5	>132	1.4	63
	2-Br	CH_3	E/Z 1:1	base	3.5	>126	2.2	79
7	2-Br	H	E	oxalate	0.6	102	0.3	20
6	2-Br	CH_3	E	oxalate	4.2	> 98	2.2	37
	2,4-di Cl	H	E/Z 1:1	base	0.5	60	0.9	82
	2,4-di Cl	CH_3	E/Z 1:1	base	2.7	42	11	63
10	2,4-di Cl	H	E	oxalate	0.5	18	2.3	73
9	2,4-di Cl	CH_3	E	oxalate	1.5	43	11	>101

Comments

The new compounds are potent inhibitors of the uptake of 5-HT and NA in brain slices. The secondary amine derivatives are generally more active than the tertiary amines. Of particular interest is the importance of the aromatic 4-substituent for producing selectivity of the uptake inhibition. It appears that the size of the substituent is determining this selectivity. Thus, the 4-iodo derivative is a completely selective inhibitor of the 5-HT uptake whereas the 4-chloro derivatives have comparable activity on the two uptake mechanisms. The 4-fluoro derivatives are slightly more active on the NA uptake. Furthermore, the 2-bromine derivatives cause a pronounced NA-uptake inhibition in contrast to the 2,4-dichloro substituted derivatives having marked 5-HT inhibitory properties. Thus, the selectivity of the compounds are dependent on the nature of the substituent as well as the position thereof.

The invention thus provides a class of compounds of great therapeutical value, by which it is possible to achieve therapeutical effect on the proposed "serotonin (5-HT)" and "noradrenaline" depressions. The compounds obtained can be relatively unselective (e.g. 4-F, 4-Cl), NA-selective (e.g. 2-Br, 3-Br) or 5-HT selective (e.g. 2,4-Cl_2, 4-I). The secondary amine derivative with a 4-chloro substituent is accordingly of great clinical interest as an unselective uptake inhibitor, which clinically should have therapeutical effect on both types of depressions.

Best mode of carrying out the invention

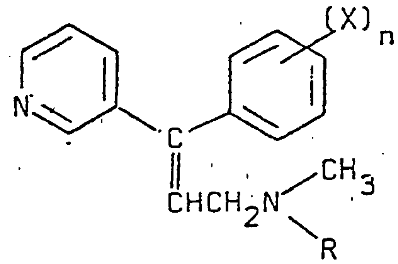
The compound 3-(2,4-dichlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine oxalate and its salts, processes for preparing said compound, pharmaceutical preparations and methods of employing said compound in therapy represent the best mode of carrying out the invention known at present.

Industrial applicability

The invention is useful in the chemical and pharmaceutical industry and in health care.

CLAIMS

1. A compound of the formula



I

or a pharmaceutically acceptable salt thereof, in which formula R is H or CH_3, n is 1 or 2 and X is a halogen selected from F, Cl, Br and I bound in an optional position to the phenyl group, provided that when X is Br it is bound in a position other than the 4 position.

2. A compound or salt according to claim 1 in the form of a geometrical isomer.

3. A compound or salt according to claim 2 wherein the pyridyl group and the amino function are in cis configuration.

4. A compound according to one or more of the preceding claims characterized in that R is H, or a pharmaceutically acceptable salt thereof.

5. A compound or salt according to one or more of the preceding claims characterized in that n is 1 and X is a halogen selected from F, Cl, Br and I bound in the 2, 3 or 4 position to the phenyl group, provided that when X is Br it is bound in the 2 or 3 position.

6. A compound or salt according to one or more of claims 1-4 characterized in that n is 2.

7. A compound or salt according to one or more of the preceding claims characterized in that a group X is bound in the 2 position to the phenyl group.

8. A compound or salt according to claim 7 selected from

3-(2-bromophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(2-bromophenyl)-N-methyl-3-(3-pyridyl)-allylamine,
3-(2,4-dichlorophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(2,4-dichlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine,

or a pharmaceutically acceptable salt thereof.

9. A compound or salt according to one or more of the preceding claims, characterized in that X represents F, I or CF_3.

10. A compound or salt according to claim 9 selected from

3-(4-iodophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
3-(4-fluorophenyl)-N-methyl-3-(3-pyridyl)-allylamine,

or a pharmaceutically acceptable salt thereof.

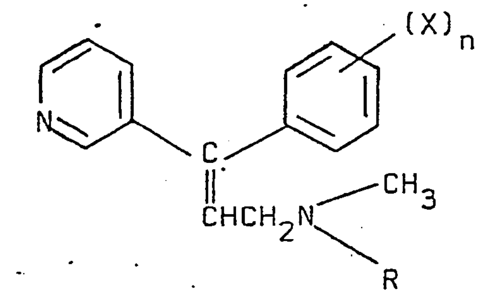
11. A compound or salt according to one or both of claims 2 to 3, characterized in that X is 3-Cl or 4-Cl and R is CH_3 and that the compound is in the form of a substantially pure geometrical isomer.

12. A compound or salt according to claim 3 selected from

Z-3-(4-chlorophenyl)-N,N-dimethyl-3-(3-pyridyl)-allylamine,
Z-3-(4-chlorophenyl)-N-methyl-3-(3-pyridyl)-allylamine, and

or a pharmaceutically acceptable salt thereof.

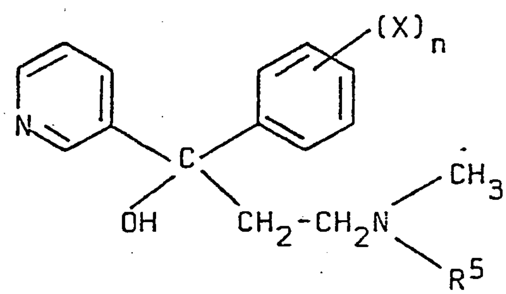
13. A process for the preparation of a compound of the formula



I

or a pharmaceutically acceptable salt thereof, in which formula R is H or CH_3, n is 1 or 2 and X is a halogen selected from F, I, Cl and Br bound in an optional position to the phenyl group as further defined in one or more of claims 1 to 11, which process comprises

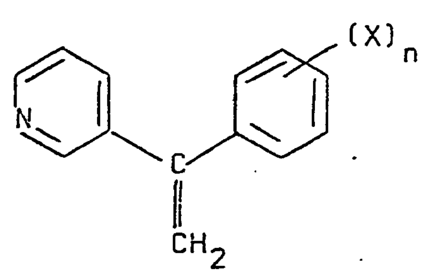
a) dehydration of a compound of the formula



II

wherein R^5 is H, CH_3 or a removable protective group and X and n are as defined above, to the formation of a compound of the formula I,

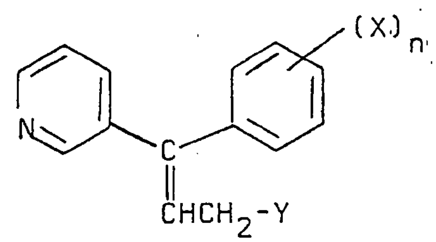
b) treatment of a compound of the formula



III

with formaldehyde and an amine of the formula $HN(CH_3)-R^2$ to the formation of a compound of formula I,

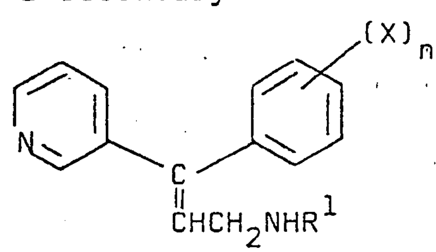
c) amination of a compound of the formula



V

wherein Y is a leaving group to the formation of a compound of the formula I,

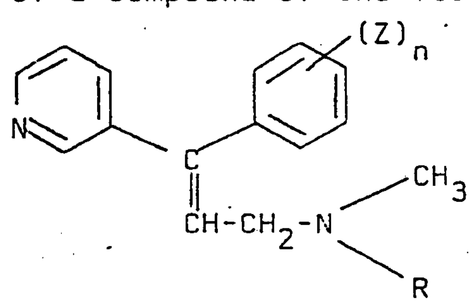
d) mono- or di-methylation of a primary amine or mono-methylation of a secondary amine of the formula



VI

wherein X is as defined above and R^1 is H or CH_3, to the formation of a compound of the formula I,

e) conversion of a compound of the formula

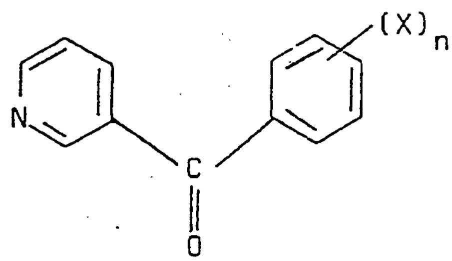


VII

wherein R is as defined above, n is 1 or 2 and Z is a replaceable moiety such as Cl, Br or I bound in an optional

position to the phenyl group, to the formation of a compound of formula I wherein X is Cl, Br or I, X being different from Z, or

f) conversion of a ketone of the formula



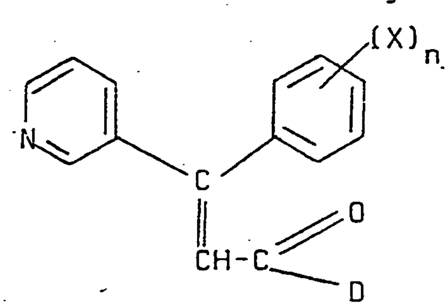
VIII

with a phosphorus ylide, prepared either in situ or presynthesized, by reaction of a compound of the formula

$$M — CH_2CH_2N\begin{matrix} CH_3 \\ R^2 \end{matrix} \qquad IX$$

whereby X and R^2 are as defined above and M is $R^3_3P^+$, $R^4_3P^+$, $(R^4O)_2P(O)$, $R^3_2P(O)$, $(R^4_2N)_2P(O)$ or $(R^4O)_2P(S)$, and R^3 is a possibly substituted phenyl group and R^4 is an alkyl group having 1-5 carbon atoms, whereby an an-ion such as a halogen e.g. Br^- is present when M is $R^3_3P^+$ or $R^4_3P^+$, with a base, to the formation of a compound of formula I, or

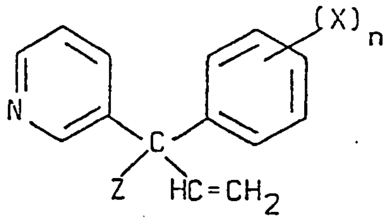
g) reductive amination of an aldehyde or carboxylic acid of the formula



X

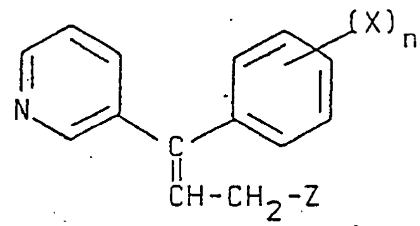
wherein D is H or OH with methylamine or dimethylamine in the presence of a reducing agent, to the formation of a compound of formula I, or

h) palladium-catalyzed amination of a compound of one of the formulas



XI

or

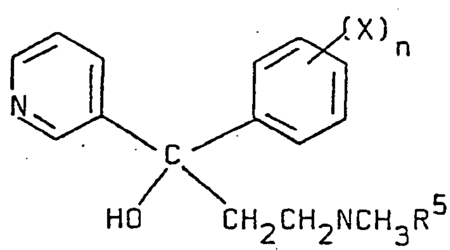


XII

wherein Z is a leaving group, with dimethylamine or methylamine, to the formation of a compound of formula I,

whereafter if desired the compound obtained by any of the methods a) to h) is converted to a pharmaceutically acceptable salt thereof and/or converted to an E or Z isomer thereof.

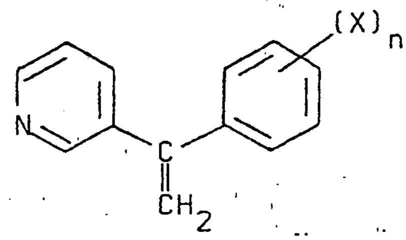
14. A compound useful as an intermediate for the preparation of therapeutically valuable compounds, which intermediate is characterized by the general formula



II

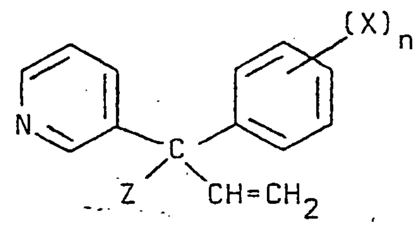
or a salt thereof, in which formula R is H or CH_3, n is 1 or 2 and X is a halogen selected from F, Cl, Br and I bound in an optional position to the phenyl group, provided that when X is Br it is bound in a position other than the 4 position,

or the general formula



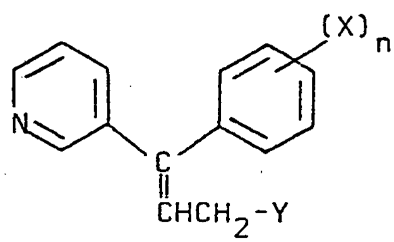
III

in which formula n and X are as defined above, or the general formula



XI

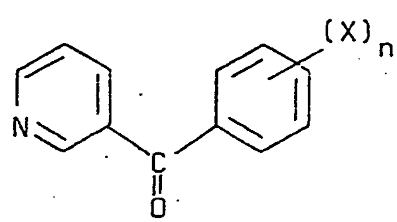
in which formula n and X are as defined above and Z is a hydroxy group, an alkoxy or alkanoyloxy group having 1-4 carbon atoms or a chlorine atom,
or the general formula



V

or a salt thereof, in which formula Y is a leaving group or OH, and n and X are as defined above,

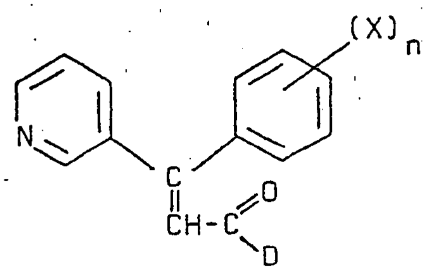
or the general formula



VIII

or a salt thereof, in which formula n and X are as defined above,

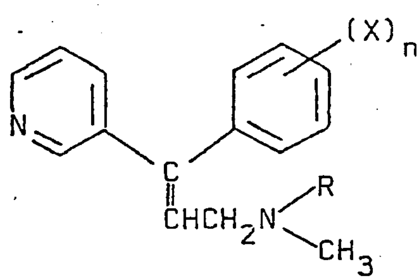
or the general formula



X

in which formula D is H or OH and n and X are as defined above.

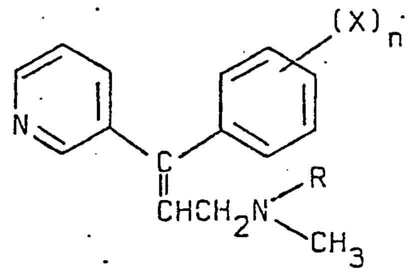
15. A pharmaceutical preparation which comprises as active ingredient a therapeutically effective amount of at least one compound of the formula



I

or a pharmaceutically acceptable salt thereof, in which formula R is H or CH_3, n is 1 or 2 and X is a halogen selected from F, Cl, Br and I bound in an optional position to the phenyl group, provided that when X is Br it is bound in a position other than the 4 position, in association with a pharmaceutically acceptable carrier.

16. A method for the treatment of depressions, characterized in administration to a host suffering from such ailment a therapeutically acceptable amount of a compound of the formula



I

or a pharmaceutically acceptable salt thereof, in which formula R is H or CH_3, n is 1 or 2 and X is a halogen selected from F, Cl, Br and I bound in an optional position to the phenyl group, provided that when X is Br it is bound in a position other than the 4 position.

17. Compounds, processes for their preparation, intermediates, pharmaceutical preparations and methods for the treatment of depressions as claimed in claim 1-16 inclusive and essentially as described.

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE80/00286

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC 3

C 07 D 213/26, 213/36; A 61 K 31/44

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
IPC 3	C 07 D 213/02, 213/04, 213/127, 213/133, 213/16, 213/18, 213/24, 213/26, 213/28, 213/30, 213/32, 213/36, 213/38, 213/44, 213/46, 213/50; A 61 K 31/44, 31/435 .../...

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
A	SE, A, 409 860 published 1979, January 5, P S Bamberg, E S Hardegger, L J S Végh	1-15
A	SE, A, 409 861 published 1979, January 5, P S Bamberg	1-15
A	SE, A, 409 706 published 1977, November 22, T O V Rydh, C B J Ulff	1-15
A	SE, A, 7605779-3 published 1977, November 22, L J S Végh, P S Bamberg, T O V Rydh	1-15
A	SE, B, 388 854 published 1976, May 24, P A E Carlsson, B SE Carnmalm, S B Ross C B J Ulff	1-15
A	SE, A, 7605573-0 published 1977, November 18, P A E Carlsson, B SE Carnmalm, S B Ross, C B J Ulff	14
X	BE, A, 781 105 published 1972, July 17, P B Berntsson, P A E Carlsson, H R Corrodi	1-15
X	EP, A, 0 000 322 published 1979, January 10, B S E Carnmalm, Th Högberg, T de Paulis S B Ross	1-15
X	FR, A, 2 206 942 published 1974, June 14, P B Berntsson, P A E Carlsson, H R Corrodi	14

.../...

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
1981-02-18	1981 -02- 26
International Searching Authority [1]	**Signature of Authorized Officer** [20]
Swedish Patent Office	Helga Treiber Helga Treiber

International Application No. PCT/SE80/00286

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

II	Continuation Fields Searched
IPC 2	C 07d 31/26, 31/28, 31/32, 31/34, 31/40, 31/42
National Cl	12p 1/01
US Cl	260:296; 546:329; 424:256, 263

V. ☐ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☐ Claim numbers ...., because they relate to subject matter [12] not required to be searched by this Authority, namely:

2. ☐ Claim numbers ...., because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. ☒ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

see 206: 1) The claims 1-13 and 15 define a novel compound and a process for its preparation
2) The claim 14 defines a novel intermediate

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

Remark on Protest

☐ The additional search fees were accompanied by applicant's protest.

☒ No protest accompanied the payment of additional search fees.

International Application No. PCT/SE80/00286

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category*	Citation of Document,[16] with indication, where appropriate, of the relevant passages[17]	Relevant to Claim No[18]
X	Chemical Abstracts vol. 46:2055c, published 1952, March 10, E Franck, K Sears	14
X	Chemical Abstracts vol. 58:9031f, published 1962, July 25, Ciba Ltd	14
X	Chemical Abstracts vol. 76:59467e, published 1971, March 26, J Nordmann, G Mattioda, J.Claverie, G. Loiseau	14
X	Chemical Abstracts vol. 86:139786e, published 1977, May 9, F Santer, P. Stanetty, A. Mesbah	14
X	Chemical Abstracts vol. 87:133285q, published 1977, October 24, U. Herzig, K. Varmuza, P. Krenmayr	14